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OBSERVATIONS ON THE COMPLEMENT FIXATION TEST FOR SYPHILIS WITH CADAVER SERUM *

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The question of the reliability of the Wassermann reaction as applied to post mortem sera, is an important one, not only from the theoretical, but also from the practical standpoint. The purpose of this paper is to review briefly the work already done along this line, and to report our own experiences with the Noguchi modification of the Wassermann reaction on sera obtained after death.

The literature bearing on the subject is nearly all German, and it is therefore in that country that there has arisen the most discussion and disagreement as to the value of the reaction. The question has hardly been touched on in American literature, and only recently in the English.

It was only two years after Wassermann made public his test that Fränkel[1] and Much (1908) published the first paper on this reaction, as applied to cadaver serum. They used several varieties of antigen, obtaining consistent results with each. Of eighty-seven cases examined, they found thirty-seven positive (42.5 per cent.). The positive results included five cases of scarlet fever. They concluded that the test was reliable and of great value in pathological anatomy. As a result of their work they considered mesaortitis certainly luetic, but sclerosis of the testicle not always so.

A paper by L. Pick and Proskauer[2] appeared about the same time. They devoted most of their attention to cases showing some anatomical evidence of lues. Cases of benign stricture of the intestine, sclerosis of the testicle, smooth atrophy of the base of the tongue, aortitis, etc., were studied, and the conclusion reached that the test was a valuable asset to pathological diagnosis.

In the same year Bruch[3] came out against the reaction. He obtained fifty-nine positive reactions in 101 cases, among them a considerable

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1. Fränkel and Much: München. med. Wchnschr., 1908, lv, 2479.
2. Pick, L., and Proskauer: Med. Klin., 1908, iv, 539.
3. Bruck: Die Serodiagnose der Syphilis, 1908, 47; Fol. Serol., 1910, iv, 395.

number in which there was no evidence of lues. He concluded that the reaction *"ist ein biologische, nicht ein cadaverische phenomenon,"* and that it was unreliable when performed with post mortem specimens. Two years later he still believed that the test could never become reliable, because the error was not one of technic, but of serum alteration. He suggested the necessity of controlling the post mortem results by reactions done during life.

In 1909, Reinhart[4] reported thirty-five cases in which the results of the reactions coincided with his clinical and anatomical findings. The reaction was positive in his cases of mesaortitis and sclerosis of the testicle.

Löhlein[5] published two papers in the same year and one in 1910. In all he covers nearly 500 cases. He obtained some anomalous negative and positive results. He admitted that there was a source of error somewhere, and was inclined to refer his positive reactions in cases giving no signs of lues, to this unknown error, rather than to latent syphilis. He thought that Bruch's results were due to the fact that the serum was not collected soon enough after death, a suggestion which Bruch partially accepted. He believed that only those cases should be considered positive in which there was complete inhibition of hemolysis. On the whole, he considered the test reliable and of value in pathological anatomy.

At the meeting of the German Pathological Society in Leipzig in 1909, at which one of Löhlein's papers was read, Schlimpert[6] expressed skepticism as to the value of the test. While acknowledging its specificity during life, he did not believe it could reach the same importance in cadavers. He reported forty-five positive results in a series of 261 cases. Nine of the positive cases gave no evidence of lues; eight, diagnosed as progressive paralysis, lacked anatomical verification; and one positive result was in scarlet fever. He acknowledged the possibility of latent syphilis in some of these cases, but thought that cachectic diseases might sometimes cause a binding of complement. He concluded that while the test was of high theoretical interest to the pathologist, it could attain a position of only limited practical significance in pathology.

Swift* examined four cadaver sera and ten spinal fluids from cadavers by both the Wassermann and the Noguchi methods, and obtained better results by the Wassermann method. No anomalous positive reactions, however, were encountered in either series.

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4. Reinhart: München. med. Wchnschr., 1909, lvi, 2092.

5. Löhlein: Verhandl. d. deutsch. path. Gesellsch., 1909, xiii, Tag. p. 92; Fortschr. d. Med., 1909, xxvii, 97; Fol. Serologica, 1910, iv, 227.

6. Schlimpert: Verhandl. d. deutsch. path. Gesellsch., 1909, xiii, Tag. p. 95.

* Swift: THE ARCHIVES OF INT. MED., 1909, iv, 376.

At a meeting of the German Pathological Society in Erlangen in 1910, Lucksch[7] reported a series of 300 cases, 50 per cent. of which were positive. In nineteen, the test was controlled by ante mortem examinations, and in each instance the two were found to coincide. He believed that a pathologist could not depend alone on a positive reaction for the diagnosis of syphilis.

In the discussion following Lucksch's paper, Lubarsch[8] reported fifty-five positive reactions in 262 cases. In sixteen of these there was no evidence of syphilis. He considered the reaction valuable, but insisted on the use of several antigens.

Schmorl[9] strongly urges that only complete inhibition be considered positive. Marchand[10] agrees with Löhlein's views, and Simmonds[11] believes that positive results in non-specific cases are due to severe cachexia, sepsis, etc.

Veszpremi[12] has published his experience in 131 cases. Of these, thirty-one had to be discarded on account of changes in the sera which rendered them unfit for use. In the remaining 100 cases, he also performed many reactions on the spinal, pericardial, pleural, ascitic and hydrocele fluids. Of the sera, 46 per cent. were positive. All but three of these agreed with the anatomical findings. The negative cases showed no clinical or anatomical evidence of syphilis. He gives a table showing the most frequent changes found in cases with positive reactions. Mesaortitis ranks first, occurring in most patients over 40 years of age; next, chronic fibrous meningitis. In simple arteriosclerosis the reaction was always negative. Mixed cases of arteriosclerosis and mesaortitis were most often found in later years (50 to 60), and gave positive reactions. In part he controlled his reactions by ante mortem tests, and found all in agreement excepting one case. The spinal fluid was never positive when the blood was negative, but in twenty-three of thirty-nine cases the blood was positive and the spinal fluid negative. The transudates agreed with the blood in about 90 per cent. of the cases. He concludes that the Wassermann reaction can afford valuable aid in the solution of some contested problems in pathological anatomy. Lucksch, however, in reviewing this work, comes to a less favorable conclusion.

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7. Lucksch: München. med. Wchnschr., 1910, lvii, 1261; Verhandl. d. deutsch. path. Gesellsch., 1910, xiv, Tag. p. 249.

8. Lubarsch: Verhandl. der deutsch. path. Gesellsch., 1910, xiv, Tag., 250. Discussion by Lucksch.

9. Schmorl: Verhandl. d. deutsch. path. Gesellsch., 1910, xiv, Tag., 250. Discussion by Lucksch.

10. Marchand: Verhandl. d. deutsch. path. Gesellsch., 1910, xiv, Tag., 250. Discussion by Lucksch.

11. Simmonds: Verhandl. d. deutsch. path. Gesellsch., 1910, xiv, Tag., 250. Discussion by Lucksch.

12. Veszpremi: Centralbl. f. allg. path. u. path. Anat., 1910, xxi, No. 5 p. 193.

Krefting[13] found that twenty-four out of ninety-six cases, in which syphilis could apparently be excluded, were positive. In another publication he found that this reaction threw valuable light on the cause of aortic insufficiency, the results of the tests corresponding almost always with the post-mortem findings.

Seligman and Blume[14] reported 100 cases. They used a number of antigens, and no test was considered positive unless there was complete inhibition of hemolysis with more than one of them. Although they had a few discordant results, they believed that the test was to be depended on, except where death was due to some wasting disease.

De Besche[15] obtained positive reactions in post mortem cases of tuberculosis, pernicious anemia and cancer. His natural inference was that the test was of a very limited value with cadaver blood.

Eich[16] investigated the problem with special reference to mesaortitis. He gave a favorable verdict.

Lubarsch[17] examined 623 sera, of which seventy-nine had to be discarded. Of the remaining 544, 109 were positive, of which forty-one gave no trace of luetic infection.

Nauwerck and Weichert[18] had to discard thirty-six of 243 sera. Of the remainder, fifty-seven were positive. They considered the method trustworthy and useful in pathological anatomy.

In October, 1911, von Werdt[19] gave a very comprehensive review of the whole question, with a full bibliography up to that time. He investigated 329 cases. Of these forty-seven were positive, 256 negative, and the rest doubtful or unsuitable for use on account of post mortem change in the serum. So he had positive reactions in 15.5 per cent. of 303 cases, a low figure compared with Bruck's 58 per cent., Lucksch's 46 per cent., and Veszpremi's 46 per cent. Of the forty-seven positive cases there were twenty-five which were probably not syphlitic. He examined many of the cases microscopically and found that there still remained a tolerable number of anomalous positive reactions after every means had been employed to discover some trace of syphilis. He concluded that if only complete inhibition be accepted as positive, and that if sera from patients with cachectic diseases be discarded, the reaction was dependable, but of restricted value.

In March, 1912, Candler and Mann[20] in London reported on their examinations of 112 spinal fluids taken post mortem. In 92 per cent.

13. Krefting: Norsk Mag. f. laegevidensk 1910, p. 65; Deutsch. med. Wchnschr., 1910, xxxvi, 366; cites Centralbl. f. Path. u. path. Anat., 1910, xxi, 354.
14. Seligman and Blume: Berl. klin. Wchnschr., 1909, xlvi, 116.
15. De Besche: Berl. klin. Wchnschr., 1910, xlvii, 1259.
16. Eich: Frankfurter Ztschr. f. Path., 1911, vii, 373.
17. Lubarsch: Jahresb. f. aerztl. Fortbild., 1911, i, 67.
18. Nauwerck: München. med. Wchnschr., 1910, lvii, 2329.
19. Von Werdt: Cor.-Bl. f. schweiz. Aerzte, 1911, xli, 993.
20. Candler: Brit. Med. Jour., 1912, i, 537.

of these the blood-serum was also investigated. Of the 112 cases of spinal fluid twenty-five were positive. All of the positive results were in cases of general paralysis, and in eight, positive reactions had been obtained during life. Three cases did not agree with the anatomical and clinical findings, but in these the spinal fluid was altered. They therefore obtained apparently correct results in 98 per cent. of the cases with the sera. They observed anomalous positive reactions in 8.3 per cent. In a case of general paralysis dying of terminal streptococcus meningitis, the spinal fluid was negative. This strain of streptococcus, when inoculated into a known positive spinal fluid, deprived it completely of inhibitory quality. They therefore considered this the cause of one anomalous result.

The same writers bring out the point that infected or decomposed spinal fluids may not only give a positive reaction in a negative case, but that under the same circumstances a known positive case may be made negative. By using 0.5 per cent. phenol as a preservative, they obtained constant results over a period of several months with the same specimen of spinal fluid. They concluded that the test is a very helpful one, but not so reliable as during life.

McIntosh and Fildes[21] in their book, gave a very concise review of the question up to 1911. They believe that some of the anomalous positive reactions are probably due to latent syphilis. As they consider post mortem sera to have more inherent power of inhibition than serum from living cases, they advise using somewhat less antigen than usual, and a control with twice the normal amount of serum alone. With these reservations they consider the test applicable to pathological anatomy.

In 1911, Wolff[22] of Amsterdam, published a paper on this subject, which was especially interesting in that it represented the first serious attempt to really discover the cause of the anomalous positive cases. Other investigators had attributed them to latent syphilis, or to changes in the serum which they did not attempt to explain. He attempted to discover the nature of this change. He was led to do this by his very bad preliminary results in which he obtained 50 per cent. of anomalous positive reactions, and found a number of sera unfit for use. He was working under unfavorable conditions, such as warm weather, lack of cold storage, etc. He showed that these anomalous positive sera contain a larger quantity of inhibiting substance than fresh normal sera. He had to use a larger quantity of complement to obtain hemolysis after these sera had been added to the hemolytic system than was necessary with normal sera, known positive luetic sera from living cases, etc.

He then found that by adding $BaSo_4$ to the sera (Wechselmann's modification of the Wassermann reaction), this inhibiting substance

21. McIntosh and Fildes: Syphilis from the Modern Standpoint. London, 1911.
22. Wolff: Ztschr. f. Immunitätsforsch., Orig., 1911, xi, 154.

could be removed without otherwise affecting the reaction. It also made possible the use of some sera which previously had to be discarded. He investigated 260 cases by both methods. There were seventeen positive cases, six of which gave no trace of syphilis. In thirty-three further cases in which syphilis could apparently be excluded, he obtained positive reactions by the original Wassermann, but negative results after the addition of barium sulphate. After considerable further experimentation as to the nature of this inhibiting substance, he decided that it was a lipoid, different from the substance causing the specific fixation of complement, but similar to the active ingredient of luetic liver extract. He believed this inhibiting substance could be removed by the use of barium sulphate, and that after such removal the test was of value in pathological anatomy. We have had no experience with this method.

From this review of previous work it is at once apparent that there is still a considerable difference of opinion as to the reliability of the test in pathological work. There are some points which we would further emphasize. In the first place, all workers have met with sera which were unfit for use and had to be discarded. Of course this makes any test impossible in such cases, and thereby imposes one restriction on the reaction in post mortem work. This condition of the serum is, in most cases, due to the time which has elapsed between death and the collection of the blood, and can accordingly be avoided in most cases by taking the serum sooner post mortem.

The limitation imposed by infection of otherwise good serum is not one which affects only the post mortem use of the test, for it is equally applicable to sera taken during life, it being well recognized that such sera give unreliable results. The anomalous negative results have not troubled investigators to any extent. They come fairly well within the range of similar results during life. In fact, the one great difficulty has been to explain the positive results in cases where syphilis could not be elicited from the history, or proven by the anatomical findings. All investigators have obtained these results. Even Wolff, who believed barium sulphate capable of removing the inhibitory substance, found that it did not do so in all cases. These anomalous positive reactions have been too frequent to permit of much faith in the theory of latent syphilis. While a few investigators have been distinctly skeptical as to the value of the test in pathological anatomy, the majority have, with certain reservations, considered it of considerable value.

Our own series of fifty-six cases is small, However, as there has been no interest shown in this phase of the Wassermann reaction in this country, and as these results represent the first reported extensive use of the Noguchi modification of the Wassermann reaction for this purpose, we believe it well to put them on record.

The cases may be divided into two groups as follows:

	Cases
1. Positive Reactions:	
Syphilitic aortitis	3
Congenital syphilis	2
Cerebral hemorrhage	1
Total	6
2. Negative Reactions:	
Acute infectious diseases	10
Carcinoma	7
Diabetes mellitus	5
Marasmus	5
Chronic diffuse nephritis	4
Chronic endocarditis	4
Tuberculosis	3
Bullet wounds	3
Fractures	2
Cirrhosis of liver	1
Lymphatic leukemia	1
Aneurysm of thoracic aorta	1
Suppurative arthritis	1
Internal hemorrhagic pachymeningitis	1
Duodenal ulcer	1
Sarcoma	1
Total	50

Of the six positive cases, five were unquestionably syphilitic, as shown by the histories and anatomical findings. The remaining case, a cerebral hemorrhage in a boy of 13, was quite suggestive. His mother had had four miscarriages. At the autopsy, an extensive hemorrhage was found in the right temporal lobe, and there was beginning atheroma of the arch of the aorta. Many large microscopic sections of the brain were studied, but they failed to show any signs of a glioma.

The histories and anatomical findings of the fifty negative cases were also carefully studied. In forty-nine there was no evidence of any kind to suggest syphilis. The remaining case deserves a little more consideration. It was a case of a large aneurysm of the thoracic aorta in a man 52 years old. There was absolutely no history of syphilis. He was under observation at the hospital over a period of three years, during which time three separate Noguchi-Wassermann reactions were found negative by three different observers. There was nothing found macroscopically or microscopically at the autopsy to suggest syphilis. As the post mortem reaction agreed with the three taken during life, it would seem that the results were perfectly reliable. In eleven of our cases, the reaction had also been done during life, and tallied in every case with the post mortem reaction. This method of controlling the reaction is the surest way of deciding on the reliability of the test.

Our work was done under favorable conditions. All but six of the cases were from the pathological department of the Presbyterian Hospital, where it was quite exceptional to have the body more than twenty-four

hours old at the time of collecting the serum. In most cases it was taken within a few hours of death, and, at times, while the body was still warm. In about five out of seven cases in which the body was more than twenty-four hours old, the serum had to be inactivated. The sixth case requiring inactivation was one of measles, and the other was the case of thoracic aneurysm, in which the serum was eleven days old at the time the test was done.

The six cases which did not come from the Presbyterian Hospital were from the morgue at Bellevue Hospital. There were also a few cases from this source which were not included in the above tables, as the sera were from bodies several days old and unfit for use. The blood was transformed from its normal structure into a thick viscid fluid, from which no serum could be separated by centrifuging.

In most of our cases the test was done within a few days of the time when the blood was taken. In only one was it postponed for over a week, and in this case inactivation was necessary. However, in this connection, it might be well to add that we have frequently found that when the active serum was kept on ice, it gave reliable results, even after two weeks standing.

In this work we have used the acetone insoluble residue of an alcoholic extract of human heart muscle as antigen. Dr. Noguchi has shown clearly that such an antigen contains less anticomplementary substance than the pure alcoholic extract. As practically all workers are agreed that one of the chief difficulties of the test lies in the increased inhibitory power of cadaver serum, it would seem particularly desirable in post mortem work to use an antigen as nearly free from anticomplementary substance as possible.

Most of the German workers have employed alcoholic extracts of syphilitic liver as antigen. We know of no previous work in which the acetone insoluble antigen has been used. Fränkel and Much's satisfactory results were obtained with an alcoholic extract of normal liver. Bruch thought that possibly the difference between his results and those of Löhlein could be rectified by their using the same antigen. He therefore substituted an aqueous for the alcoholic extract, but still obtained the same unreliable results. Seligman and Blume used aqueous and alcoholic extracts of both syphilitic and normal livers. We believe that the acetone insoluble antigen is preferable for this work, and that its use will eliminate many of the discordant positive results.

Another factor of perhaps greater importance is the condition of the serum. As we have seen, in some cases, usually in subjects no longer fresh, the test cannot be done at all, as the blood has been transformed into a thick, grumous mass from which no serum can be obtained. In other cases, where the serum separates normally from the clot, it is

nevertheless infected, and, as with sera from living subjects under similar circumstances, the results are not dependable.

There is still another class of cases in which there is no visible change in the serum, but in which, nevertheless, there develops anticomplementary power in varying degrees. It is with these cases that investigators have had the greatest difficulty, and on account of which the test has been, by some, condemned. While we feel confident that the use of the acetone insoluble antigen in our cases has, to some extent, eliminated the difficulties inherent in these sera, we believe that it is important that more work be done to determine the nature of this inhibiting substance. A few of our cases needed inactivation on this account, but were perfectly satisfactory after the serum had been heated. In this small series of fifty-six cases our results have been most satisfactory. There is only one possibly anomalous positive result, that of the cerebral hemorrhage in a boy of 13 years. From our experience with the test we are inclined to the belief that the positive result in this case is strong confirmatory proof of the syphilitic nature of his disease.

In conclusion we may say that in the testing of cadaver blood—

1. The use of the acetone insoluble residue of alcoholic antigen is preferable on theoretical and practical grounds, to the pure alcoholic or aqueous extracts, for the reason that less anticomplementary substance is introduced.

2. The serum to be tested should be collected from the cadaver as soon as possible after death, and the test performed at the earliest possible date.

3. Infected and decomposed serum, from either the cadaver or the living subject, is not suitable for the complement binding test.

4. In this series of fifty-six cases, the Noguchi modification of the Wassermann test has given very reliable results.

STUDIES OF RENAL FUNCTION IN RENAL, CARDIORENAL AND CARDIAC DISEASES*

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Renal function has been studied in fifty-seven patients, the cases including pure nephritis, cardiac and cardiorenal diseases, the tests used being phenolsulphonephthalein, lactose, salt, water, potassium iodid and the accumulation in the blood of uncoagulable nitrogen. In certain cases, the excretion of indigo carmin and rosanilin was studied, as was also the glycosuria following the injection of phloridzin. It became apparent early that nothing was to be gained from the continued use of these dyes, as they were excreted roughly in proportions paralleling the excretion of phthalein and both much more slowly. Moreover, they were irritating to the patients. The use of indigo carmin was discarded also, because its colorimetric properties are not well adapted to accurate quantitative work.[1] The glycosuria following the administration of phloridzin seems to bear some relation to the excretion of lactose under similar conditions, i. e., glycosuria is prolonged. Phloridzin glycosuria, however, is exceedingly variable under any conditions and it was considered more advantageous to use only lactose, on which greater reliance can be placed.

These tests were used with the following objects in view: (1) To estimate total renal function; (2) to determine the absolute and relative value of these tests in the diagnosis and prognosis of renal diseases; (3) in cardiorenal disease with varying degrees of chronic passive congestion and nephritis, to determine more accurately which factor is of greater importance in the causation of the clinical picture encountered; (4) to diagnosticate the presence or absence of impairment of renal function in cases in which clinically nephritis is suggested; (5) finally, to determine whether it is justifiable to draw conclusions relative to the involvement of the vascular or tubular functions under pathological conditions. In the majority of cases a limited number of tests were made. It is hoped that the cases will be followed over a longer period of time, and that repeated tests will be made to determine the progress of the disease. Such results will be published later.

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1. In this connection we agree with Oppenheimer (Ztschr. f. Urol., 1909, iii, 289), and disagree with Thomas (Am. Jour. Med. Sc., 1911, cxlii, 376).

A brief outline of the purpose of the various tests, together with their technic, is given.

Phenolsulphonephthalein was introduced in 1910 as a functional test by Rowntree and Geraghty.[2] It is a drug devoid of toxicity and is eliminated almost entirely by the kidney. In health, following its intramuscular injection (.006 gm.), 50 to 60 per cent. is recovered in the urine in one hour and from 60 to 80 per cent. in two hours.

From a study of a large series of cases including acute and chronic parenchymatous and chronic interstitial nephritis, and uremia, they concluded that where there was a marked decrease in output, marked renal changes were present. When the drug was continuously excreted in traces or not at all a grave prognosis was to be given, even without signs of uremia. The test proved of immense value in revealing the degree of destruction of renal substance, and of extreme importance in the estimation of total renal function for diagnosis and prognosis.

The test has been made according to the original technic.

TECHNIC

Patients were injected intramuscularly with 1 c.c. of a sterile solution containing 0.006 gm. of the drug. Each patient's bladder was emptied at the end of one hour and ten minutes and at the end of two hours and ten minutes. The urine was made definitely alkaline, diluted to 1 liter, and the amount of drug present determined by the use of Rowntree and Geraghty's[3] modification of the Autenrieth-Königsberger colorimeter.

Lactose Test.—Schlayer[4] and his coworkers have studied the excretion of lactose, potassium iodid, salt and water in relation to renal function in experimental tubular and vascular nephritides, and in nephritis as exists clinically.

Lactose was shown by Voit[5] to be excreted quantitatively by the kidneys following its subcutaneous or intravenous administration. De Bonis[6] showed that it was well excreted by the glomeruli. Schlayer therefore adopted the time required for its elimination as a means of determining the vascular functional capacity in various forms of experimental and clinical nephritis. Since it is a substance foreign to the body, and consequently not subjected to the many extra renal factors which influence the excretion of water, he places his chief reliance on it as a vascular functional test. He admits that its excretion is delayed in passive congestion.

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2. Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1909, i, 579.
3. Rowntree and Geraghty: The Archives Int. Med., 1912, ix, 284.
4. Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1910, xcviii, 17; Schlayer: ibid., 1911, cii, 311, and 1911, ci, 333.
5. Voit: Deut. Arch. f. klin. Med., 1897, lviii, 545.
6. De Bonis: Giorn. intern. d. science med., 1907, xxix, 446.

As De Bonis did not claim that lactose was not excreted by way of the tubules, but merely that it was well excreted by the glomeruli, it seemed advisable to study more closely the mechanism of its excretion. As shown by Nussbaum[7] it is possible by excluding the glomerular system to obtain a urine from the frog's kidney which is solely due to tubular activity. By using this method we have shown in another publication that the tubules in the absence of the glomerular system are capable of excreting lactose.

From a repetition of Schlayer's experimental work, from our own experience with lactose clinically as a functional test and from our recent studies of its behavior in experimental chronic passive congestion,[8] we feel that the mechanism of its excretion differs essentially from that of phthalein, salt, indigo, carmin, etc. In these studies, therefore, we have considered lactose, as did Schlayer, an index to the condition of the vascular function of the kidney, admitting that we need much more information concerning the manner and significance of its excretion.

In these studies lactose has been prepared and injected as follows:

Two and five-tenths gm. were dissolved in 25 c.c. of freshly distilled water placed in small cotton stoppered Erlenmeyer flasks and pasteurized for four hours for four successive days at 75 to 80 C. By this method the dose injected was slightly over 2 gm. in 20 c.c. of water. A fresh solution was used for each injection and given according to the usual intravenous technic. Following injection no constitutional disturbances resulted save occasional slight headaches or malaise and in one instance a severe chill and fever for a few hours.

The normal excretion time for this amount is four to six hours. The urine was collected from the patients four hours after injection and every hour or two hours thereafter to twelve hours. Each specimen was tested by Nylander's reagent, using the same amounts of urine, solution, and length of time for boiling. In addition, in our earlier studies, polarimetric readings were made for total amounts of sugar regained. Since Schlayer emphasized the time required for excretion as of chief importance, more recently we have merely determined this except where only traces were obtained.

Salt and Water Tests.—The excretion of salt following its administration in amounts greatly in excess of that ordinarily taken with the food, is accomplished by the tubules, according to Schlayer. Normally large amounts of salt are excreted by one of two methods. If the salt is given without extra water it is almost entirely excreted within twenty-four hours, without diuresis, by increased concentration in the urine; if given with an excess of water it is excreted partially through increased concentration in the urine and partially through diuresis.

Where vascular injury to the kidney exists, the administration of salt may be followed by a marked diuresis, all of the salt being smoothly excreted in twenty-four hours without its percentage content in the urine

7. Nussbaum: Pflüger's Arch. f. d. ges. Physiol. 1878, xvi, 179; 1878, xvii, 580.

8. Rowntree, Fitz and Geraghty: Unpublished.

being at all increased. This is usually associated with a somewhat low and fixed specific gravity, and the syndrome is spoken of by Schlayer as vascular hyposthenuria. Here the inability to concentrate is not due to any incapacity of the tubules to excrete salt, but to hypersensitive vessels which respond to the salt administration with diuresis. In more severe vascular injury the vessels do not react in the same way, oliguria characterizing the urinary picture. In severe tubular destruction, a urine of fixed low specific gravity is obtained, the quantity of which is not materially affected by the administration of salt and the salt content of which is not augmented by administration of extra amounts of chlorids because of the inability of the tubules to excrete it. Such a condition Schlayer calls tubular hyposthenuria.

The tests were performed as follows:

At the beginning of each study the patient was put on restricted liquids (2,000 c.c.) and a diet low in chlorids. A few cases were tried on salt-poor diet, e.g., 2.4 gm. per diem, but it was found that immediately following this extra salt was usually poorly excreted, while the same patients on a diet containing more salt, e.g., 5 gm. per diem later responded to added salt normally. The salt in the diet was estimated approximately by Locke's[9] and Brugsch's[10] tables. The urine was measured as passed, and total twenty-four hour specimens collected. The specific gravity was taken, and daily salt analyses made by the Lütke-Martius[11] method. When the salt output was found to be approximately constant for two days, in suitable cases, a salt test of from 5 to 10 gm. was given. In this way when produced, a hyposthenuria and its type could be detected.

Potassium Iodid Test.—Potassium iodid was one of the first substances to be utilized in connection with functional renal studies, being introduced by Duckworth[12] in 1867. It appears quickly in the urine following its administration by mouth, Quetsch[13] stating that it appears in nine to eighteen minutes after a 2 gm. dose, Roux[14] thirteen minutes after a 3 gm. dose, and Studeni[15] thirteen to eighteen minutes after a 1 gm. dose. The time required for complete elimination, as stated by different authors, varies markedly. According to Geisler,[16] 6 gm. require twenty-five hours; Roux,[14] 5 gm. require thirty hours; Studeni,[15] 1 gm. requires thirty to thirty-six hours, Antem,[17] .5 gm. requires forty hours, Schlayer and Takayasu[18] and Monokow,[19] .5 gm. requires forty-eight

9. Locke: Food Values. D. Appleton & Co., 1911.
10. Brugsch: Diätetik innerer Erkrankungen. Berlin, Julius Springer, 1911.
11. Sahli: Diagnostic Methods, 1911, p. 455.
12. Duckworth: Saint Bartholomew's Hosp. Rep., 1867, iii, 216.
13. Quetsch: Berl. klin. Wchnschr., 1884, xxi, 353.
14. Roux: Thèse de Paris, 1890, No. 248. Experiences sur l'elimination des jodures par l'urine.
15. Studeni: Untersuchungen über die physiologische Ausscheidung der jod Preparate durch den menschlichen Harn. Dissert., Zurich, 1897.
16. Geisler: Quoted by Anten. (See Note 17.)
17. Anten: Arch. f. Pathol. u. Pharmacol., 1902, xlviii, 331.
18. Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1911, ci, 354.
19. Monokow: Deutsch. Arch. f. klin. Med, 1911, cii, 248.

hours. Schlayer, in his studies, did not consider, however, anything less than sixty hours to be a delayed excretion time following .5 gm. by mouth. We have accepted this as a standard.

According to the studies of Schlayer, potassium iodid is excreted by the tubules of the kidney and on it he has placed most dependence in determining tubular functional capacity. Anten[17] showed that the excretion is not hastened by the occurrence of diuresis. It has been claimed by Schlayer and Takayasu that its excretion is not influenced by chronic passive congestion and that it is not delayed in cases of cardiac decompensation, characteristics which, if true, would make it of tremendous importance in differentiating cases of pure passive congestion of the kidney from passive congestion associated with nephritis. Our studies,[8] however, on the excretion of potassium iodid in experimental chronic passive congestion show that it is often delayed in this condition. We feel, therefore, that for this purpose it is practically valueless.

Five-tenths gm. of potassium iodid was given by mouth. Urine was collected at the end of forty-eight hours and tested every four hours thereafter until no positive Sandow's[20] test could be obtained.

Determination of the Incoagulable Nitrogen of the Blood.—In 1821, Prevost and Dumas[21] found after extirpation of the kidneys an increase in the urea content of the blood. That this observation was of importance clinically in nephritis was recognized by Bright[22] in 1836. Since then many investigations have been made with the object of using the total incoagulable nitrogen or urea as a guide to prognosis and diagnosis.

By more modern technic, Ascoli[23] Strauss[24] and others have found in severe grades of nephritis, the nitrogen, usually though not invariably, increased, the increase being much more marked toward death. Müller[25] believes that these facts in outspoken uremia are of the highest value, while von Noorden,[26] emphasizing the inconstancy of the findings, admits that the accumulation of nitrogen constitutes one of the important phenomena which result from renal insufficiency.

Obermayer and Popper[27] have found that cases of uremia show a

20. Sandow's test is made by taking 30 c.c. of urine, 2 c.c. of 2 per cent. sodium nitrite solution and 2 c.c. of dilute sulphuric acid, adding chloroform and shaking. Purplish or violet color appears in the chloroform if iodid is present.

21. Prevost and Dumas: Quoted by Schöndorff. Pflüger's Arch. f. d. ges. Physiol., 1899, lxxiv, 307.

22. Bright: Guy's Hosp. Rep., 1836, i, 358.

23. Ascoli: Pflüger's Arch. f. d. ges. Physiol., 1901, lxxxvii, 103.

24. Strauss: Die chronische Nierentzündungen in ihrer Einwirkung auf die Blutflüssigkeit und deren Behandlung. Berlin, 1902, Hirschwald.

25. Müller: Verhandl. der deutsch. path. Gesellsch., 1904-5, vii-ix, Ergänzungsheft 80.

26. Von Noorden: Metabolism and Practical Medicine, 1907, ii, 486.

27. Obermayer and Popper: Ztschr. f. klin. Med., 1909, lxvii, 332.

much higher serum incoagulable nitrogen content than do normal individuals, or cases of nephritis without uremia, and that of this nitrogen, the urea fraction increases with the development of the uremia. Hohlweg[28] points out the importance of this latter observation, agreeing that though increase in urea is not specific for uremia, the demonstration of its presence in excessive amounts in serum affords an index of the renal functional capacity and thus is of value prognostically. Widal,[29] from an accumulation of his own observations in renal insufficiency, believes that it is generally possible to base on the degree of urea retention an approximate prognosis as to length of life, since patients persistently with more than 2 gm. of urea per liter of blood can usually live for only months or weeks.

In attempting to choose a method for estimation of incoagulable nitrogen or urea which is clinically practical, e. g., simple, rapid and reasonably accurate, we have used and compared the following tests on blood or blood-serum:

1. Estimation of urea in blood by Widal's method: 10 c.c. of blood are added to 115 c.c. of 95 per cent. alcohol; 100 c.c. of the filtrate is evaporated to dryness, and the residue dissolved in the least possible amount of water. This is tested for substances decomposable by sodium hypobromite in a Doremus ureometer.[30] The amount determined represents that found in 8 c.c. of blood, from which the amount per liter is calculated.

2. The technic is the same as above, except that the residue following the evaporation of the filtrate is subjected to a Kjeldahl's nitrogen determination. The result represents that found in 8 c.c. of blood.

3. Estimation of total incoagulable nitrogen in serum by Morris'[31] modification of the Hohlweg and Meyer method. The procedure is as follows: To 10 c.c. of serum in a 300 c.c. Erlenmeyer flask is added a reagent consisting of equal parts of 1 per cent. acetic acid and a 5 per cent. solution of monocalcium phosphate until the reaction is acid to litmus but neutral to congo red. The volume is brought up with distilled water to 80 c.c., and 80 c.c. of saturated sodium chlorid solution are poured into the flask. The mixture is boiled to precipitate the coagulable proteins, and the filtrate, from which the proteins have been shown to be completely removed, subjected to a nitrogen determination by Kjeldahl's method.

In a number of instances determinations were made by all three methods. The two latter gave nearly similar results. It was found that the first method in a control series of experiments, adding known amounts of urea to serum, gave an error of from 10 to 60 per cent., and therefore as a quantitative test was valueless.

Blood was used rather than serum (save in cases in which venesection was made), because it seemed that any increase of value prognostically would appear in the total blood as well as in serum. In the majority of cases Method 2 has been used. The normal figures are for total incoag-

28. Hohlweg: Deutsch. Arch. f. klin. Med., 1912, civ, 216.
29. Widal: Bull. et mém. d. hôp., Paris, series 3, 1911, xxxii, 627.
30. Widal used the Yvonne ureometer for this purpose.
31. Morris: The Archives Int. Med., 1911, viii, 457.

ulable nitrogen .500 to .600 gm. per liter, and for urea .300 to .500 gm. per liter of serum.[32]

In the present state of our knowledge of renal diseases, classification of nephritis is difficult and unsatisfactory, and none so far suggested has met with universal acceptance or approval. Although clinically in certain instances it is possible to recognize acute, chronic parenchymatous or chronic interstitial nephritis, the autopsy findings repeatedly reveal processes different from those suggested in life. The internist is therefore inclined to confine his diagnosis to acute or to chronic nephritis; but even under such conditions the pathological study frequently demonstrates the presence of acute or chronic changes which were not suggested by the clinical study or history of the case, so classification on clinical-pathological grounds alone has proven unsatisfactory.

From his studies with the lactose, water, salt and iodid tests, Schlayer[4] has attempted to divide nephritis from a purely functional point of view

TABLE 1.—CASES OF

Hosp. No.	Age	Clinical Diagnosis	Fluids	Urine	Sodium Chlorid			Sp. Gr.	Lactose (Hrs.)	Iodid (Hrs.)
					In	Out	Per cent.			
82,337	57	Arteriosclerosis; chronic nephritis? Good condition.	1600	1400	3.4	3.6	.26	1012	6	48
			1630	1425	10	9.1	.64	1022	...	..
82,437	43	Brain abscess; hemorrhagic pachymeningitis; grave condition.	....	....	.....	.....	.....	†	5.5	48
			....	....	.....	.....	.....	....	...	..
83,410	17	Orthostatic albuminuria;* chronic nephritis?	1540	1555	10	10.4	.67	1013	6.5	36
			2500	1760	18	16.4	.93	1020	...	..

*It is a question whether this case should not be placed in Group II. †Variable. ‡Few hyaline casts.

into four groups, e. g., pure vascular, vasculo-tubular, tubulo-vascular, and pure tubular nephritis. We have not used his classification because we feel that it is open to serious objections on the following grounds: (1) Our studies have led us to the conclusion that the potassium iodid test as used by him and on which he has placed greatest confidence for information regarding tubular functional capacity, is unreliable. (2) He has not described, nor have we encountered, any clinical cases which could be justly considered pure tubular nephritis. (3) The tests used cannot, we believe, determine accurately in the majority of cases where both systems are involved, whether the tubular or vascular injury is preponderant. (4) Mild passive congestion alone will in many instances produce the same functional picture which he describes as characteristic of vascular nephritis. Hence a combined clinical and functional study is

32. The technic in this test must be subjected to considerable refinement before conclusions based on slightly increased values (25 to 30 per cent.) can be drawn.

essential in order to differentiate two functionally similar but clinically different conditions. (5) Schlayer has purposely not considered cases in which cardiac involvement was present. Since chronic nephritis is so commonly associated with cardiac or cardiovascular changes, whether causally or incidentally, we feel that in making a study of renal function, this group of cases should be considered.

Therefore, attempting to correlate clinical and pathological findings with the results of functional tests as simply and comprehensively as possible, the cases studied have been divided as follows:

Group I.—Cases clinically suspected of nephritis[33] but exhibiting practically normal renal function.

Group II.—Cases of mild nephritis without cardiac decompensation.

Group III.—Cases of advanced nephritis without cardiac decompensation.

Group IV.—Cases of the cardiac decompensation and chronic passive congestion with or without nephritis.

SUSPECTED NEPHRITIS

Phthalein		Urinalysis			B. P. Sys.	Nitrogen Blood	Urea Blood	Remarks
1 Hr.	2 Hr.	Alb.	Blood	Casts				
40	70	0	0	‡	220	.3	.3	Renal function normal; patient left hospital improved.
..	..	..	..					
50	70	+	0	§	110	..	..	Renal function normal; tests done to exclude nephritis; patient left hospital improved.
..	..	..	..		170	..	..	
40	55	+	0	0	125	..	.5	Patient left hospital with condition unchanged.
..	..	..	..					

§Occasional casts.

Besides these groups we have studied a few miscellaneous cases each of which will be described in detail (Group V).

GROUP I

It is seen from Table 1 that in these cases the increased salt is excreted normally almost completely within twenty-four hours through an increased concentration in the urine. The specific gravity is not fixed. Lactose and iodid are excreted in normal time, the phthalein output is not decreased, while the incoagulable nitrogen of the blood is within normal limits.

These cases are of interest in showing the value of such studies in renal function diagnostically. A brief history of each is given.

33. The clinical diagnoses recorded in the accompanying tables were taken from the Johns Hopkins Hospital case records.

No. 82,337. Male, 57, white, married, entered the hospital with the following history:

He had always worked hard in business, with considerable worry. His habits were excellent. Three years before admission he was told that he had "diabetes." At intervals since various physicians had found sugar in his urine. For years he had noticed slight nycturia. He entered the hospital because, for six months, he had lost weight and strength and had been growing nervous.

Physical examination was negative save for moderate cardiac hypertrophy, with an accentuated aortic second sound, and a soft systolic bruit transmitted from the apex to axilla. His peripheral vessels showed a considerable degree of sclerosis. His blood-pressure was 220.

The urine showed no albumin or casts, but a trace of sugar, which immediately disappeared under slight carbohydrate restriction.

In brief, his was a case in which nephritis might be legitimately suspected, and if existent, to determine its degree would be of essential importance for prognosis, diagnosis and future treatment. Functional tests showed normal renal function, hence the conclusion that his symptoms were due to arteriosclerosis, from which, so far, the kidneys had escaped to such a degree that function was not disturbed.

No. 82,437. A Russian tailor, 43, married, was admitted with the following history:

Eight days before entry he had suddenly felt dizzy and fallen. Since, he had had fever and sweating, considerable frontal headache, and a dry cough without sputum. At times he was delirious, at times in stupor.

Physical examination was negative save for a few fine crackles heard in both axillae on deep inspiration, absence of knee-jerks, a positive Romberg's sign, and questionable Babinski's. On the right there was a marked choked disk; on the left were scattered hemorrhages with the edges of the disk obliterated. The blood-pressure varied between 110 and 170.

The urine showed a trace of albumin and rare casts. There was a temperature between 101 and 103 F.

While the signs and symptoms pointed toward an intracerebral lesion, it was of utmost importance to demonstrate conclusively the entire absence of nephritis, or if any injury to renal function were present, that it was too slight to be responsible for the symptom-complex. From functional studies there was no evidence of nephritis. The patient gradually improved, and left the hospital with the diagnosis of brain abscess or hemorrhagic pachymeningitis.

No. 83,410. Boy, 17 years old, entered the hospital with a diagnosis of "orthostatic albuminuria." His mother died of some renal disease.

His previous illnesses included chicken-pox and measles. Until six months previously he had had constant "sore throat" which was relieved by tonsillectomy. His habits were good.

On admission he complained of frequent headaches, vertigo, nausea and vomiting of ten months' duration.

His physical examination was negative except for distinctly palpable peripheral vessels. His blood-pressure was 125 mm. Hg.

A trace of albumin was found in the urine, intermittently, but no blood-cells or casts were seen.

As indicated in the accompanying table (Table 1), his renal function was practically normal, the only suggestion of disturbance being the slightest delay in lactose excretion and a phthalein output slightly under the lower limits of normal. He is grouped among patients with normal function, tentatively. Repeated observations in such cases are unquestionably indicated, and it is hoped that further reports on these cases may be offered later.

GROUP II.—CASES OF MILD NEPHRITIS

Nephritis in this group of cases is suggested clinically by some increase in blood-pressure, a slight cardiac hypertrophy, and palpable peripheral vessels, while albumin and casts may or may not be present in the urine. Functionally, the phthalein test indicates that the total renal excretory function may be normal, but is usually slightly decreased. A delay in lactose excretion, however, suggests vascular disturbance of function which may be corroborated by the associated "vascular hyposthenuria" following the administration of salt. The specific gravity may or may not be fixed. The absolute salt excretion as well as that of iodid is usually normal. There is slight or no increase in the urea of the blood.

Opportunity has not been afforded to follow any one of these cases over a prolonged period of time, but it appears justifiable to suppose that such cases, if progressive, develop eventually into cases either of cardio-renal disease, or of marked chronic nephritis, i. e., Group II may pass over into Group III or Group IV. The data relative to these patients is presented in Table 2. Two characteristic cases are quoted.

Mr. X, aged 22, student, consulted Dr. F. J. Sladen, resident physician of the Johns Hopkins Hospital, on account of cardiac palpitation. Patient's father and uncle had died of nephritis. His previous history was unimportant, his habits good. Six months before examination patient noticed attacks of cardiac palpitation. Physical examination revealed a slightly enlarged heart, definitely thickened peripheral vessels, an occasional extrasystole, and a maximal blood-pressure varying from 140 to 150 mm. Hg. The urine showed at times the faintest trace of albumin but no casts were seen.

Functional studies showed normal phthalein, iodid and salt excretion, with a markedly delayed lactose. The urea of the serum was not increased.

No. 82,837. Male, 55, chemist, entered the hospital with an unimportant family and previous history. He had always worked hard and worried. His habits were excellent.

For some years he had noted nycturia, polyuria and mild attacks of nocturnal dyspnea. For one month he had felt "weak" and dull.

Physical examination showed that his heart was enlarged on percussion, with a rather heaving impulse. There were no murmurs. The aortic second sound was not increased. The peripheral vessels were thickened, with some atheromatous patches, and were tortuous. The fundi oculorum were negative. The urine showed no albumin or casts. The systolic blood-pressure was 166.

Functional studies showed a slightly reduced phthalein (40 per cent. in the first, 12 per cent. in the second hour), a distinct diuresis following the increased ingestion of salt and a slight delay in lactose excretion, 10 hours.

Clinically these cases were instances of arteriosclerosis, but from functional studies it was shown that the total renal function in one, as indicated by phthalein excretion, was slightly affected, in the other normal; the delay in lactose excretion suggested vascular involvement, and diuresis in response to salt in one case that the vessels were hypersensitive. On the whole, these were cases of arteriosclerosis in which it was justifiable to assume that pathological changes had occurred in the kidneys, primarily of a vascular nature, but sufficient to interfere to some extent with some phase of renal function.

GROUP III.—CASES OF ADVANCED NEPHRITIS WITH BUT SLIGHT CARDIAC INVOLVEMENT (TABLE 3)

As already suggested, there is no sharp line of differentiation between this group and Group II, since in chronic cases there is a gradual transi-

TABLE 2.—CASES OF

Hosp. No.	Age	Clinical Diagnosis	Fluids	Urine	Sodium Chlorid			Sp. Gr.	Lactose, Hrs.	Kl., Hrs.
					In	Out	Per cent.			
X	22	Arteriosclerosis, nephritis	1500	1000	9	8	.8	1020	10	48
82,931	47	Chronic nephritis	1220	870	5	.74	.20	1015	10	48
			1140	1200	14	3.6	.30	1010	..	..
82,643	24	Chronic nephritis	1430	800	3	3.3	.43	1012	6	40
			1140	700	9	7.0	1.00	1023	..	..
82,837	55	Chronic nephritis, arteriosclerosis	1120	1800	7	7	.39	1011	10	48
			1360	2170	15	13	.59	1012	..	..

*Patients all left the hospital with improvement of symptoms. †Rare. ‡At times.

tion from the early stages of nephritis into this group or Group IV. Our acute cases, without doubt, must be included here on account of the results obtained by functional studies.

In this group, clinically, there was evidence of marked nephritis, but none of cardiac inefficiency. The changes in renal function are therefore dependent on nephritis and not on chronic passive congestion.

The cases varied in severity. They have been grouped to show, as far as possible, the gradual transition from nephritis with nearly normal renal function, to the most severe grades exhibiting uremia and ending in death.

In every case the excretion of water was either relatively or absolutely increased by additional salt, with three exceptions, and in only one was oliguria encountered. Certain of the cases were not given additional

salt, since from the clinical condition it seemed contra-indicated. In the cases tested, as a rule, salt was relatively well excreted through both increased concentration and polyuria. But in cases of the most advanced type it was constantly excreted in amounts less than administered and at the same time in low concentration. The specific gravity tended to be "fixed" and moderately low, except in one case.

Lactose excretion was delayed in all cases. In all but the most extreme cases there seemed to be no definite relationship between the excretion time of lactose, the severity of the disease clinically and the vascular hypersensitiveness, as determined by response to salt.

Potassium iodid excretion was delayed in the severest cases, but to an equal extent in two, which clinically were less advanced. Its excretion time did not seem to parallel absolutely the phthalein excretion nor the salt concentration, since the two cases in which the iodid was most slowly

MILD NEPHRITIS*

Phthalein		Urinalysis			B. P. Sys.	Nitrogen, Blood	Urea, Blood	Remarks
1 Hr.	2 Hrs.	Alb.	Blood	Casts				
60	80	‡+	0	0	150	..	.176	No cardiac decompensation.
..	62	+	..	†	130	..	.700	Patient on salt poor diet for a long time. No cardiac decompensation.
30	51	+++	..	+	130	..	.275	Received lactose intramuscularly. Amount recovered not estimated. No cardiac decompensation.
40	52	0	..	0	166	..	.370	No cardiac decompensation.

excreted increased the salt concentration, following an additional 5 gm. to the diet, and one excreted 45 per cent. of phthalein in three hours.

As the disease became more advanced the excretion of phthalein constantly diminished. In patients with uremia, repeatedly, it was excreted only in traces or not at all for the two hours following injection.

The total incoagulable nitrogen and urea were increased in those cases which clinically and functionally had the most severe nephritis. Unfortunately, in one of the patients coming to autopsy no determination was made.

In five patients no lactose was recovered within twelve hours. Of these the four which were tested were unable to excrete salt either through increased concentration or through diuresis. Two showed a normal iodid excretion and two an excretion markedly delayed; four excreted only

TABLE 3.—CASES OF CHRONIC NEPHRITIS

Hosp. No.	Age	Clinical Diagnosis	Fluid	Urine	Sodium Chlorid			Sp. Gr.	Lactose Hrs.	Iodid, Hrs.
					In	Out	Per cent.			
81,952	42	Chronic nephritis with acute exacerbation.	1380	1145	2.4	3.80	.32	1012	8	48
			1380	1065	7.4	8.17	.76	1024	†	..
82,917	57	Chronic nephritis; mitral stenosis	1220	700	4.00	5.1	.77	1015	12	48
			1220	675	9.00	7.4	1.10	1017	..	..
Y	45	Chronic nephritis	1000	920	10	9.2	1 —	1018	10	48
			....	....	.....	.....	.....	....	..	..
81,691	55	Chronic nephritis	2640	2400	.....	.....	.....	1012	*6	..
			1960	2260	.....	.....	.....	1016	..	..
82,203	45	Chronic nephritis; brain tumor	1200	690	2.4	2.7	.40	1017	12+	48
			800	730	7.4	6.3	.87	1016	..	..
82,020	51	Chronic nephritis; arteriosclerosis	1640	1350	2.4	1.4	.11	1013	*6	57
			1360	1300	7.4	3.00	.22	1014	..	..
81,331	8	Acute and chronic nephritis; mitral insufficiency; chronic tonsillitis	860	1000	5.00	3.00	.30	1010	9	40
			480	400	3.00	.89	.28	1015	..	..
81,567	51	Chronic nephritis; mitral insufficiency and myocardial insufficiency	1440	960	5 —	5—6	.59	1020	12	..
			960	1460	12 —	13.5	.93	1017	..	..
81,586	34	Chronic nephritis	2680	2350	9 —	9.4	.40	1005	17	68
			3660	3320	12 —	13.2	.40	1003	..	..
81,541	28	Chronic nephritis	960	2350	8 —	8.2	.35	1012	12	84
			1390	1550	4 —	5.0	.31	1014	..	..
81,813	50	Chronic nephritis	1060	1500	2.4	1.5	.10	1012	12+	96
			1160	2400	7.4	5.5	.23	1010	..	..
80,891	24	Chronic nephritis; typhoid fever with hemorrhages from bowel and nose.	1660	2030	10 —	12 —	.60	1009	10	48
			1980	1860	8 —	8 —	.42	1012	..	..
		Pyelitis; urethritis	2000	1650	5 —	7 —	.42	1006	0	48
			2000	1700	10 —	6.8	.40	1006	..	..
82,358	52	Myocardial insufficiency; arteriosclerosis; chronic nephritis; uremia.	....	....	.....	.....	.....	....	0	48
			....	....	.....	.....	.....	....	..	..
81,578	50	Chronic nephritis; uremia; arteriosclerosis	920	1640	8 —	3 —	.18	1012	0	72
			1290	1225	5 —	2 —	.16	1015	..	..
90,899	64	Chronic nephritis; arteriosclerosis; myocardial insufficiency; uremia	940	1050	7 —	2.7	.26	1016	0	72
			1110	1100	5 —	2.8	.26	1012	..	..
81,667	43	Acute nephritis; ulcerative endocarditis	1000	580	1 —	.87	.15	1012	0	..
			1000	760	1 —	1.60	.21	1009	..	..

*In one of these cases only a trace of lactose was recovered during these six hours. Where no quanti present only in traces within the six hours and later not at all. †Trace. ‡Three hours. §Rare.

WITHOUT CARDIAC DECOMPENSATION

Phthalein		Urinalysis			B. P.	Nitrogen in Blood	Urea in Blood	Remarks
1 Hr.	2 Hrs.	Alb.	Blood	Casts				
15	45	+	+	+	180—	.600	.500	Left hospital improved.
..	..	..	..	..	140	.....	.....	
..	42	+	..	+	180	.....	.850	Left hospital improved.
..	..	..	..	..	...	.....	.....	
25	40	..	..	..	208—	.....	.....	Untreated.
..	..	..	..	..	140	1.3	.800	.....
..	38	0	0	0	170	.....	.300	The amount of lactose recovered not determined quantitatively. Untreated in hospital.
..	..	..	..	..	...	.....	.....	
..	37	+	..	+	270	.....	.600	Left hospital improved.
..	..	..	..	..	...	.....	.....	
..	37	+	0	+	190—	.728	.600	The amount of lactose recovered not determined quantitatively. Left hospital improved.
..	..	..	..	..	160	.....	.....	
8	34—	++	+	+	80—	.....	.....	Phthalein repeated in 8 weeks showed 10 per cent. for 1 hour; 30 per cent. for 2 hours. Left hospital improved.
..	..	..	..	..	140	.....	.....	
24	35	++	..	+	260—	.....	.300	Heart compensated. Left hospital improved.
..	..	..	..	..	190	.....	.....	
17	27	+	§	+	240	.400	.....	Left hospital improved. Died six months later. No autopsy.
..	..	..	..	..	...	.....	.....	
†	45%	+	+	+	200—	.400	.....	Patient had edema. Left hospital unimproved.
..	‡	..	..	..	130	.....	.....	
5	7	+	..	+	210—	.....	.....	Left hospital improved.
..	..	..	..	..	160	.....	.....	
5	10	+	..	+	160	.....	.500	Second test two months after the first. Left hospital improved.
..	..	..	..	..	...	.....	.....	
—	†	+	..	+	...	.....	1.4	.....
..	..	..	..	..	...	.....	.....	
†	10	+	..	+	230—	.....	1.85	At the time of test heart was compensated. Left hospital unimproved.
..	..	..	..	..	270	.....	.....	
0	0	++	..	+	150—	.....	.500	Urea was determined 8 weeks later and was 1.40. Repeated phthalein test showed always traces for 2 hours. Patient died in uremia. No autopsy.
..	..	..	..	..	180	.....	.....	
0	0	+	0	+	230	.....	.....	When test made heart was recompensated. Two months earlier phthalein was 13 per cent. for 2 hours. Autopsy 3664. Chronic diffuse nephritis with an acute exacerbation.
..	..	..	..	..	...	.....	.....	
..	†	+	+	+	110	.....	1.20	Autopsy 3681. Acute ulcerative endocarditis. Acute diffuse nephritis. Healing kidney infarcts.
..	..	..	..	..	...	.....	.....	

tative study has been made an excretion period of six hours may be misleading since lactose may be

traces of phthalein, the other, 10 per cent., for two hours. In four the incoagulable nitrogen or urea was markedly increased. In the fifth it was not tested. The three patients with lowest phthalein died, two in uremia within a few weeks, and one immediately with acute nephritis. The others have not been heard from.

The histories of a few characteristic cases are given.

No. 81,952. Housewife, aged 42, entered with the following history:

Her previous history was unimportant save that three years before she had been in the hospital for three weeks with acute and chronic nephritis. Since then she had suffered from mild nycturia, precordial distress on exertion, and occasionally from headache.

Two weeks before entry edema suddenly developed, associated with severe vomiting. The urine became scanty and cloudy.

Physical examination showed a markedly hypertrophied heart. The aortic second sound was ringing, no murmurs heard. There was marked sclerosis of peripheral vessels and slight edema of the legs but no general anasarca or fluid in the serous cavities. The blood-pressure was 180. Urine at first was smoky, with blood, albumin and casts. Under rest this cleared up, leaving a slight trace of albumin and a few casts.

Her functional studies showed only a trace of lactose excreted in eight hours, though iodid and salt were normal. That total function was affected was shown by a lowered phthalein output (15 per cent. for one hour; 45 per cent for two hours). The urea in the blood was not increased. Hence functionally as well as clinically she had well marked renal involvement which was not of great immediate significance. In the hospital her symptoms disappeared and she left much relieved.

No. 80,891. Laborer, aged 24. For several years he had been bothered by nycturia; otherwise was always well.

Three weeks before entry he had been sick with fever, anorexia and nausea.

Physical examination was negative save for a faint systolic murmur at the apex of the heart not transmitted to the axilla. The peripheral vessels were readily palpable. The blood-pressure was slightly increased (140 to 160). The urine contained traces of albumin and a few casts.

The typhoid bacillus was obtained from blood-culture. The Widal reaction became positive.

The patient ran a severe and protracted course of fever, which was complicated by hemorrhages from the nose and bowel, reducing his hemoglobin to 18 per cent.

Eight weeks after entry his renal function was tested. It was found that the patient had a constant polyuria and "hyposthenuria" with salt normally excreted as to concentration and absolute amount. Lactose was excreted in ten hours, and 10 per cent. of phthalein in two hours. The potassium iodid was excreted normally; there was no nitrogen increase in the blood. From the lactose and phthalein tests, evidently the patient had a severe nephritis.

A week later the temperature, which had been normal for ten days, suddenly rose and ran an irregular course for several days. A pure culture of typhoid bacilli was grown from the urine.

Six weeks later the patient had a severe attack of pain in the right flank, with vomiting and fever. This subsided and was followed by an abundance of pus in the urine, disappearing in a few days.

The tests for renal function were repeated. It was found that iodid was excreted normally; salt, however, was retained, with no change in concentration on the addition of 5 gm. Lactose was not recovered at all, and phthalein only in traces two hours after injection. The urea of the blood had trebled. Functionally his condition had grown markedly worse, confirmed clinically.

Two weeks following the attack described the patient had another similar one but more severe, which was accompanied by delirium, fever and marked abdominal pain localizing in the region of the right kidney. This again subsided, accompanied by pyuria.

Ureteral catheterization was performed. Clear urine was obtained from both sides. Cultures from the right side showed the typhoid bacillus.

Finally, five weeks after the first attack of pain, the patient had a third similar one. It seemed advisable to operate. The kidney was exposed under ether and incised, but no recognizable pus was obtained. The patient improved rapidly, and was discharged in excellent condition. Unfortunately he has not been heard from since.

No. 90,899. Laborer, aged 64. Three years previously he was told that he had nephritis. Since then he had noticed nycturia and polyuria.

One month before entry he began to lose weight rapidly and become easily tired. Constant headache developed, and very recently shortness of breath. He noticed swelling in his feet for the first time at entry.

His physical examination revealed an enlarged area of cardiac dulness, with gallop rhythm at the apex, and a soft systolic blow over the aortic area. The aortic second sound was sharply accentuated. The peripheral vessels were markedly thickened and tortuous. The fundi were normal. There was slight edema of the extremities. The blood pressure was 190 to 230. The urine showed much albumin and many casts. The phthalein was 13.6 per cent. for two hours.

Under observation and rest the edema disappeared, and the heart practically regained compensation. The general condition grew worse, however. Six weeks after the first test, functional tests were again made, showing only traces of phthalein excretion in two hours, no lactose in twelve hours and a delayed excretion of iodid and salt. The patient died in typical uremia. The diagnosis of nephritis was confirmed at autopsy.

Thus in cases of pure nephritis these tests are of value diagnostically in determining impairment of renal function, when clinically it is merely suspected. They are of value prognostically, for by repetition, especially of the phthalein test, it is possible to determine whether the disease is progressing, remaining stationary or subsiding. Moreover, patients with nephritis who continue to be unable to excrete phthalein, or lactose, and who show marked difficulty in excreting iodid and salt, usually die within a short time. Marked increase of the incoagulable nitrogen of the blood may afford additional positive evidence as to the severity of the disease.

GROUP IV.—CASES OF CHRONIC PASSIVE CONGESTION WITH OR WITHOUT ASSOCIATED NEPHRITIS (TABLE 4)

The majority of our patients fall into this group. In so classifying them, a consideration of both clinical findings and functional studies is necessary in order to determine the relative responsibility of the heart and of the kidney for the existence of the symptom-complex. In this connection repetition of the tests is almost invariably necessary. One series of functional tests cannot always differentiate between the existence of nephritis or of chronic passive congestion. Experimentally,[8] it has been shown that in moderate degrees of passive congestion, as in nephritis, the excretion of lactose, iodid and salt may be interfered with. The excretion of phthalein may be normal, but if the congestion is extreme, it

TABLE 4.—CASES OF CARDIAC DECOMPENSATION AND CHRONIC

Hosp. No.	Age	Clinical Diagnosis	Fluid	Urine	Sodium Chlorid			Sp. Gr.	Lactose, Hrs.	KI, Hrs.
					In	Out	Per cent.			
82,121	48	Chronic nephritis; arteriosclerosis; angina pectoris; myocardial insufficiency	800 900	600 600	2.4 7.4	1.2 3.2	20 54	1023 1023	10 ..	48 ..
82,216	47	Myocardial insufficiency. Aortic insufficiency. Arteriosclerosis. Chronic nephritis?	1200 1280	830 945	2.4 2.4	8.3 7.5	1 .81	1023 1021	Trace in 4 hrs.: none later	72
82,731	48	Myocardial insufficiency. Mitral reg. and stenosis?	1200 1270	1015 1900	10 18	10.6 17.1	1.0 .90	1017 1019	8 ..	.. ..
82,755	49	Myocardial insufficiency. Arteriosclerosis. Mitral insufficiency	1420 1500	815 1005	5 10	6.5 11	.86 1.1	1022 1026	6 ..	48 ..
82,152	64	Myocardial insufficiency; myocarditis; arteriosclerosis	825 1025	1420 1350	2.4 2.4	15.6 16.2	1.1 1.2	1020 1021	7 ..	.. ..
82,914	53	Myocardial insufficiency; arteriosclerosis; nephritis	....	....	....	....	....	....	12+ ..	48 ..
81,600	64	Arteriosclerosis; myocardial insufficiency	1260	780	6	11.7	1.5	1023	8 ..	48 ..
81,304	38	Myocardial insufficiency; mitral insufficiency; chronic nephritis	1430 1240	1835 1400	8 12	22.5 16	1.21 1.21	1012 1015	Trace 5 ..	48 .. ..
81,384	35	Myocardial insufficiency; myocarditis; arteriosclerosis	1250 1250	615 680	2.4 5.4	3.5 4.5	.57 .66	1030 1018	8 ..	60 ..
82,012	54	Myocardial insufficiency; mitral reg. and stenosis; arteriosclerosis	1085 1200	980 810	7.4 2.4	6.2 4.2	.63 .52	1014 1021	12 ..	86 ..
82,179	60	Myocardial insufficiency; myocarditis; arteriosclerosis; chronic nephritis?	1600 1600	880 830	7.4 2.4	3.6 3.5	.42 .43	1019 1020	12 ..	48 ..
82,670	59	Myocardial insufficiency; chronic nephritis; arteriosclerosis	1525 1350	540 510	5 10	2.7 5	.51 .93	1020 1021	9 ..	48 ..
81,513	64	Chronic nephritis; arteriosclerosis; myocardial insufficiency; cirrhosis of liver	960 960	150 1275	7 5	6.3 2	.60 .15	1015 1013	12 ..	60 ..
81,543	49	Myocardial insufficiency; aortic insufficiency; arteriosclerosis	1200 1200	1126 954	5 7	4.6 4.5	.41 .48	1010 1020	9 ..	68 ..
81,544	73	Myocardial insufficiency; syphilis; arteriosclerosis; mitral stenosis; myocarditis; chronic nephritis	1240 1240	1550 2300	8	9.7	.63	1016 1014	10	.. .. ..
82,392	45	Chronic nephritis; arteriosclerosis; myocardial insufficiency	1210 1150	865 425	7.4 2.4	2.6 .72	.27 .17	1017 1021	12+ ..	48 ..
82,367	48	Myocardial insufficiency; mitral stenosis and regurgitation	....	....	....	....	....	....	12+ ..	48 ..

PASSIVE CONGESTION WITH OR WITHOUT NEPHRITIS

Phthalein		Urinalysis			B. P.	Nitrogen in Blood Gms.	Urea in Blood Gms.	Remarks
1 Hr. Per cent.	2 Hrs. Per cent.	Alb.	Blood	Casts				
47	79	+	..	+	170	.6	.7	Left hospital improved.
..	..	..	..	..	...	.....	.....	
56	76	+	..	Gran.	180	.....	.....	Left hospital improved.
..	..	..	..	..	130	1.6	1.2	
51	70	+	..	0	160	.....	.....	Left hospital improved.
..	..	..	..	..	180	.....	.....	
..	25	+	..	Rare	150	.....	.5	Second phthalein test two weeks later. Left hospital improved.
..	70	..	..	..	...	.....	.....	
32	54	0	..	0	120	.....	.....	Left hospital improved.
..	..	..	..	..	150	.....	.6	
..	47	+	..	+	180	.....	.6	Left hospital improved.
..	..	..	..	..	130	.....	.....	
22	47	..	..	..	200	.....	.8	Left hospital improved.
..	..	0	..	0	2	.....	.....	
..	..	..	..	..	160	.....	.....	
34	46	+	At first but	Few	170	.....	.5	Left hospital improved.
..	..	..	Clearing	..	140	.....	.....	
..	..	..		..	1	.....	.....	
..	47	0	..	Few	120	.....	.....	Left hospital unimproved.
..	..	..	..	..	...	.....	.....	
23	45	+	..	+	180	700	.6	Eight weeks later phthalein 45 per cent. for 2 hours. N .600. Left hospital improved.
..	..	..	..	..	...	.....	.....	
8	16	+	..	Rare	170	1.3	.8	Left hospital improved.
..	3 weeks	..	..	..	120	.....	.....	
..	45	..						
..	40	+	..	+	180	.....	.....	Left hospital improved.
..	..	..	..	..	120	.....	.3	
..	22	+	..	+	150	.....	.6	Patient died four months later. Autopsy 3766, tubercular polyserositis, arteriosclerosis, cardiac hypertrophy, slight chronic diffuse nephritis.
..	10 weeks	..	..	..	180	.....	.....	
..	32	..						
17	37	0	..	Rare	150	.....	.3	Phthalein 22 per cent. for 2 hours eight weeks later, after a break in compensation. Patient died. Autopsy 3738: syphilitic aortitis, cardiac hypertrophy and dilatation; chronic passive congestion of abdominal viscera. Kidneys showed slight increase in connective tissue between the tubules and thickening of Bowman's capsule.
..	22	..	..	..	...	.....	.....	
19	35	0	0	Rare	140	.....	.....	Patient left hospital improved.
..	..	..	..	..	1	.....	.....	
..	..	..	..	..	180	.....	.....	
17	34	+++	..	+	200	.....	1.	Patient left hospital unimproved.
..	..	..	..	..	...	.....	.....	
5	36	+	..	+	116	.....	.8	Patient left hospital improved.
..	..	..	..	..	140	.....	.....	

TABLE 4.—CASES OF CARDIAC DECOMPENSATION AND CHRONIC

Hosp. No.	Age	Clinical Diagnosis	Fluid	Urine	Sodium Chlorid			Sp. Gr.	Lactose, Hrs.	KI, Hrs.
					In	Out	Per cent.			
82,803	50	Myocardial insufficiency; mitral insufficiency; dilated aortic arch; arteriosclerosis	....	....	.....	.....	.....	....	12+	48
			....	....	.....	.....	.....	....	..	..
81,590	53	Myocardial insufficiency; mitral stenosis? Dilated aortic arch. Pulsus irregularis perpetuus	1870	1055	5	12.4	1.18	1030	8	48
			1470	1275	8	15.3	1.2	1020	..	..
			....	....	.....	.....	.....	....	..	..
82,382	50	Arteriosclerosis; myocardial insufficiency; chronic nephritis?	....	....	.....	.....	.....	....	10	100
			....	....	.....	.....	.....	....	..	..
			....	....	.....	.....	.....	....	..	..
82,923	56	Chronic nephritis and acute exacerbation; arteriosclerosis; myocardial insufficiency	1320	1425	8	5.7	.40	1021	0	48
			1620	1425	8	5.1	.37	1020	..	3
			....	....	.....	.....	.....	....	1 wk. later	15
			....	....	.....	.....	.....	....	1 wk. later	25
81,861	58	Arteriosclerosis; myocardial insufficiency; myocarditis; arteriosclerosis	1550	2550	13	16	.6	1020	10	..
			1270	775	8	9	.6	1027	..	..
			....	....	.....	.....	.....	....	..	..
82,303	43	Myocardial insufficiency; arteriosclerosis; chronic nephritis; uremia	1310	1006	3	5	.50	1017	0	48
			1000	1000	3	8.5	.85	1017	..	..
82,782	64	Myocardial insufficiency; arteriosclerosis; chronic nephritis	1220	700	4	5.1	.77	1076	12	48
			1220	675	9	7.4	1.1	1076	..	..
82,732	49	Arteriosclerosis; glycosuria; chronic nephritis; myocardial insufficiency	1080	1425	15	14	1.	1016	..	54
			860	775	5	2	.....	1022	..	..
81,055	48	Myocardial insufficiency; arteriosclerosis; chronic nephritis; dextrocardia	1570	1025	5	5.4	.54	1021	12	48
			1320	1075	7	6.4	.60	1011	..	..
81,242	55	Myocardial insufficiency; chronic nephritis	1260	1760	7	4	.23	1016	12	72
			1500	1715	5	3.7	.22	1006	..	..
			....	....	.....	.....	.....	....	..	..
81,899	44	Arteriosclerosis; chronic nephritis; cardiac hypertrophy and dilatation	1700	1775	24	31	17	1010	0	..
			1780	1620	74	34	21	1014	..	..
			....	....	.....	.....	.....	....	..	..
81,161	46	Chronic nephritis; uremia; myocardial insufficiency	900	1160	8	6.2	54	1012	0	72
			1000	1450	10	8.0	56	1008	..	..

PASSIVE CONGESTION WITH OR WITHOUT NEPHRITIS—Continued

Phthalein		Urinalysis			B. P.	Nitrogen in Blood Gms.	Urea in Blood Gms.	Remarks
1 Hr. Per cent.	2 Hrs. Per cent.	Alb.	Blood	Casts				
18	27	+	+	+	130	.....	.7	Patient left hospital unimproved.
..	..	..	..	..	160	.....	.....	
..	30	+	0	+	130	.....	.3	Patient left hospital improved.
..	..	..	..	..	1	.....	.....	
..	..	..	..	..	160	.....	.....	
7	32	+	0	+	210	500	600	Patient left hospital improved.
..	..	..	..	..	1	.....	.....	
..	..	..	..	..	160	.....	.....	
27	44	+++	+	Hyal. &	160	1.	1.2	Patient left hospital improved.
..	..	..	..	Gran.	1	.....	.....	
..	..	..	..	..	140	.....	1.3	
..	..	..	..	..	...	.....	.....	
15	27	+	0	Rare	170	.....	.6	Patient left hospital improved.
..	...	..	..	..	1	.....	.....	
..	..	..	..	..	160	.....	.....	
0	Trace	+	..	+	216	.63	.6	Second phthalein test three weeks later. Autopsy 3707: chronic subacute nephritis, chronic passive congestion.
13	..	..	..	..	...	.....	.....	
..	24	+	..	+	220	.....	.400	Patient left hospital improved.
..	..	..	..	..	180	.....	.....	
17	27	+	0	+	?	.....	.81	Lactose not given on account of glycosuria. Patient left hospital improved.
..	..	..	..	..	...	.....	.....	
7	20	+	0	+	150	.....	.3	Patient left hospital improved.
..	..	..	..	..	120	.....	.....	
0	Trace	+	0	Few	200	.....	1.40	Died. No autopsy permitted. Second phthalein 10 days after first; third test after three weeks.
15	30	..	..	..	1	.....	.....	
18	28	..	..	..	220	.....	.....	
12.5	20	+	0	+	170	2.8	2.5	Patient left hospital improved.
5	10	..	..	..	1	.....	.....	
15	—	..	..	..	200	.....	.....	
0	0	++	..	+	180	.....	.....	Died. Autopsy 3664: Chronic diffuse nephritis with acute exacerbation. Cardiac hypertrophy and dilatation.
..	..	..	..	..	150	.....	.....	

may be decreased. Therefore, in experimental congestion, functional pictures indistinguishable from those of Group II and III described above have been found. The gradual amelioration of experimental congestion is accompanied earliest by an increased phthalein output, later by improvement in salt and iodid excretion, and lastly by a slight amelioration of the delayed lactose excretion.

Clinically, in passive congestion the tests behave in a similar way. By studying Table 4, it is seen that in certain cases the functional results are identical with those obtained in an entirely different group (Groups II and III). It is seen that lactose is invariably delayed. Hence this test in such cases is of slight value. The specific gravity is not fixed, the quantity of urine varies depending on the degree of cardiac compensation. The excretion of salt varies. In certain cases there is retention; in others more salt is excreted than ingested, either with "hyposthenuria" or increased concentration, or both. Potassium iodid, as a rule, is excreted normally even when nephritis is marked. Its excretion has been delayed strikingly, however, in four cases, in three of which the cardiac insufficiency played the major rôle. The fourth at autopsy showed an advanced nephritis. In these cases with congestion and little or no nephritis the phthalein excretion is nearly normal, but as congestion becomes more marked it is decreased, returning nearly to normal with surprising rapidity as the cardiac conditions improve. If, however, there is a coexistent nephritis the phthalein excretion remains low, and does not improve markedly, despite improvement of circulation. In any case of nephritis with marked cardiac involvement, lactose, water, salt and iodid are vitiated as tests for renal function. By repeating the phthalein injection, however, information of great value may be obtained. *In the presence of marked nephritis the excretion of phthalein will remain low,* paralleling the degree of renal destruction. In those instances in which the excretion of phthalein is normal, or where after a decrease due to passive congestion, it has again become normal, nephritis may be entirely absent.[34]

In this class of cases the determination of nitrogen retention may be of value. According to Strauss and Hohlweg, incoagulable nitrogen and urea are increased in chronic passive congestion, but not so strikingly as in nephritis. Therefore, any marked increase gives valuable confirmatory evidence of extensive renal involvement.

The cases studied have been arranged in the table so as to show instances of pure chronic congestion and of slight nephritis, moderate

34. Such cases, particularly if exhibiting a normal salt excretion at the same time, may constitute a class of "Pure Chronic Passive Congestion." In our studies we have not described such a group, because we feel that clinical observations and functional studies should be made over a prolonged period before the existence of mild grades of nephritis can be excluded.

nephritis or advanced nephritis complicated by varying degrees of cardiac insufficiency and chronic passive congestion. A few illustrative cases are described.

No. 82,216. Laborer, 47 years old, entered with an unimportant family history. Previously he had rheumatic fever, gonorrhea and syphilis (confirmed by a positive Wassermann reaction). At times he was a heavy drinker.

For ten years he had constant nycturia. For a year he had complained of dyspnea on exertion, with increasing weakness. For a month his feet were swollen. He entered the hospital because he was unable to keep up any longer.

Physical examination revealed a diffuse, heaving cardiac impulse, with area of dulness markedly increased. A systolic murmur was heard over the precordium, loudest at the apex, and transmitted to the axilla. Along the left border of the sternum was a diastolic murmur of slightly different pitch and intensity. The sounds at the base were soft. The second pulmonic sound was louder than the second aortic. The chests were dull at the bases and numerous râles were heard.

The fundi were negative. Albumin and casts were present in the urine at entry. The blood-pressure was 180. On the whole this seemed to be a typical case of cardiorenal disease, in which clinically it was difficult to determine the degree, if existent, of nephritis. Functional studies showed salt put out in larger amounts than taken in without diuresis, delayed iodid excretion, only a trace of lactose recovered. The phthalein output was, however, normal. From functional studies, therefore, there was disturbance in vascular function, with a normal total excretory function. Therefore clinically and functionally the patient showed marked cardiac weakness, with slight nephritic involvement. The subsequent history supported this view. The blood-pressure fell to 130, and the albumin and casts disappeared from the urine; the patient was discharged greatly improved.

No. 82,755 represents another case of this description. The patient was a fishman, 49 years old. His father died of "heart trouble." The patient had always been well until a year before entry when his heart became irregular. Three months before entry he grew short of breath on exertion, the condition growing worse. Recently he had noticed nycturia and "swelling of his feet" during the day, which disappeared over night. He entered the hospital because he was unable to work any longer.

Physical examination showed a markedly hypertrophied and dilated heart, with an apical systolic murmur transmitted to the axilla. The peripheral vessels were markedly sclerosed. Examination of the chest showed dulness over both lower backs suggesting a moderate effusion. The liver was enlarged and tender. There was marked edema of extremities and genitalia. The urine showed albumin and rare casts. The blood-pressure was 150.

His functional tests showed no polyuria, salt well excreted by increased concentration, iodid normally excreted, lactose found only in traces for six hours, and none later. The phthalein was 25 per cent. for two hours. Clinically the case seemed chiefly cardiac. A repeated phthalein test ten days later showed 70 per cent. for two hours. In the meantime the albumin and casts had disappeared. The patient grew steadily better. Thus from a combined clinical and functional study it was clear that nephritis was absent, or if present, playing but a slight part in the clinical picture.

These cases bring up an interesting consideration. The delayed lactose and iodid excretion may be the result of cardiac weakness, and thus these cases may be of purely cardiac involvement without nephritis. This can only be determined by repeating the tests when compensation has been perfectly established.

No. 81,242 is a case of undoubted nephritis, combined with cardiac insufficiency. The patient was a tailor, 55 years old. His family and previous history were negative, save for two attacks of gonorrhea in youth.

Ten to fifteen years previously he had noticed spells of palpitation associated with weakness and giddiness. For several years he had complained of nycturia, and had been short of breath on exertion.

Eight months before entry he began to have attacks of nocturnal dyspnea, gradually followed by tenderness referred to the liver, and edema of the legs. For two months he had noticed marked loss of appetite and nausea.

The heart was markedly enlarged to percussion. A faint systolic murmur was heard along the left border of the sternum. The second pulmonic sound was slightly more accentuated than the aortic, both with a ringing note. The peripheral vessels were sclerosed. The lungs showed signs of diffuse bronchitis. The liver edge on percussion was 5 cm. below the costal margin, not felt on account of the marked tenderness. There was edema of the extremities and over the sacrum. The urine showed a large amount of albumin and casts. The blood-pressure was 220.

At the time the salt and water tests were made the patient showed a constant diuresis, with inability, however, to excrete salt. Lactose and iodid were delayed in excretion, phthalein was put out only in traces, the urea in the blood was increased. Thus functionally and clinically the patient was suffering from a failure of cardiac compensation, with marked nephritis. Under treatment cardiac compensation was largely regained. The lactose, however, remained delayed, the phthalein showed a slight relative increase, but persistently remained far below normal (never becoming more than 30 per cent. for two hours), and urea in the blood did not diminish. The patient died. Unfortunately no autopsy was permitted.

No. 82,923 is very similar. A laborer, 56 years old. His family and previous history were negative so far as known.

Two weeks before entry the patient was suddenly seized with chilliness, followed by precordial distress and cough. Three days later swelling of the legs was noted.

Physical examination showed an enlarged heart with marked arhythmia. There were no murmurs. The aortic second sound was ringing. There was marked sclerosis of the peripheral vessels and edema of the legs which shortly disappeared. The blood-pressure was 160. The urine showed albumin and casts in abundance.

Functional tests showed no polyuria, salt well excreted, and iodid normal. No lactose was excreted in twelve hours; 44 per cent. of phthalein for two hours. The urea of the blood was markedly increased. A week later the phthalein dropped to 30 per cent. for two hours, and two weeks later to 10 per cent. for two hours. The general condition had not improved, the patient showing toxic symptoms. After bleeding and sweating he became more comfortable and the phthalein rose to 25 per cent. for two hours. He improved clinically under rest, his phthalein, however, not increasing.

No. 82,303 is a case of advanced nephritis with cardiac dilatation and uremia. The patient was a barber, 43 years old.

His father had died of "dropsy and asthma." In his youth the patient had "children's diseases." For the past four years he had been a heavy drinker.

For six months he had noticed nycturia. For two weeks before entry he had suffered from "nocturnal dyspnea" which had finally become constant, and was accompanied by rapid onset of general edema.

Physical examination revealed a cyanosed, dyspneic man. The cardiac impulse was diffuse, heaving, and the area of dulness increased. A blowing systolic murmur was heard at the apex, transmitted to the axilla, and a murmur of different pitch and intensity at the base, transmitted to the vessels of the neck. A pericardial friction sound was heard at the xyphoid cartilage. The peripheral vessels were markedly sclerosed.

In the chest were heard numerous scattered rales. The liver was readily felt and was tender. There was marked edema of the extremities and sacrum, slight of the face and genitalia. The blood-pressure was 216 to 200.

Functional tests showed that urine was excreted in the same amounts as the fluid intake, with salt excreted in excess of the intake. Iodid excretion was normal. No lactose was recovered, and only a trace of phthalein in two hours. The nitrogen of the blood was not increased. Clinically and functionally the case suggested advanced nephritis with cardiac decompensation.

The patient's cardiac condition improved. The phthalein rose slightly (to 13 per cent. for one hour). A month after this observation the patient suddenly developed convulsions and died. Unfortunately no functional tests were repeated, save a determination of total nitrogen in the serum, which was not increased.

Autopsy showed cardiac hypertrophy and dilatation, with marked chronic passive congestion and advanced subacute and chronic nephritis.

This case is interesting in showing that nitrogen determinations of the blood-serum may not be of value when negative, agreeing with the observations of Strauss,[24] who constantly found low figures in patients with chronic parenchymatous nephritis who died of uremia.

No. 81,161 is a similar case. Laborer, 40 years old.

His previous history included measles, mumps and occasional attacks of tonsillitis.

For eight years the patient had been short of breath on exertion, and twice had had swelling of his feet.

He entered the hospital for gradually increasing dyspnea, orthopnea and edema.

The heart was enlarged on percussion; no murmurs heard. The aortic second sound was accentuated. The peripheral vessels were readily palpable. The lungs gave signs of diffuse bronchitis. There was shifting intra-abdominal dulness, and edema of dependent parts. The urine showed large amounts of albumin and casts. Blood-pressure varied between 180 and 150.

Functional tests showed frank polyuria, with salt fairly excreted. The excretion of iodid was, however, markedly delayed, and no lactose or phthalein were recovered. Therefore, functionally the patient had a marked nephritis. That nephritis was the important picture was supported by the facts that despite rest in bed and cardiac improvement, the phthalein was not excreted. The patient died with symptoms of uremia. The diagnosis of nephritis and cardiac insufficiency was confirmed at autopsy.

On the whole, studies of renal function in such cases are of the utmost value. If considered along with the clinical picture, and repeated at intervals, they furnish most valuable information regarding the relative responsibility of the heart or kidney in producing the clinical condition.

GROUP V.—MISCELLANEOUS CASES

The cases in this group appeared atypical from the point of view of nephritis both clinically and functionally. The clinical diagnoses were cases of suspected syphilitic nephritis, of suspected amyloid nephritis, of nephrolithiasis, of polyserositis, and of carcinomatosis with Bence-Jones albumosuria. Each case is presented in detail.

No. 81,373. Housewife, aged 27.

Her family and previous history were unimportant. She entered with a history of cough for two months, accompanied by shortness of breath, disturbances in

vision, nycturia, and loss of weight. Physical examination revealed a heart not enlarged, with a faint apical systolic murmur not transmitted to axilla or back. The lungs showed a slightly dull right apex over which were heard numerous coarse râles. The abdomen and extremities were not remarkable. From the facts that no tubercle bacilli were found in the sputum, that the Wassermann reaction was positive, and that at entry there was albumin and casts in the urine, it seemed possible that the renal condition might be syphilitic.

The functional studies are as tabulated. The patient was able to excrete salt and lactose normally, but the phthalein was only 38 per cent. for two hours. Iodid was not given, since the patient was receiving the drug medicinally. However, under treatment the phthalein in a month was 60 per cent. for two hours, the general condition had improved markedly, there were no longer casts or albumin in the urine. Therefore, it does not seem justifiable to class this patient among nephritics.

No. 79,832. Laborer, 30 years old.

TABLE 5.—

Hosp. No.	Age	Clinical Diagnosis	Fluid	Urine	Sodium Chlorid			Sp. Gr.	Lactose, Hrs.	Iodid, Hrs.
					In	Out	Per cent.			
81,373	27?	Syphilitic nephritis; acute bronchitis; tuberculosis?	1010	1305	8	7.5	58	1013	5	..
(1)			1060	700	6	4.4	63	1020	..	..
79,832	30	Syphilitic arthritis; amyloid nephritis?	1560	1100	10 —	9.40	.86	1016	12+	50
(2)			2220	1355	13 —	13.50	1.00	1012	..	..
82,004	42	Nephrolithiasis; renal colic; arteriosclerosis	1700	620	5 —	4.1	67	....	4	36
(3)			1500	855	10 —	6.00	71	....	..	..
81,925	32	Splenic anemia; polyserositis	1500	1200	8 —	6.6	55	....	..	..
(4)			1500	1250	13 —	5.5	46	....	5	50
82,971	35	Carcinomatosis	1040	900	5	1.3	15	1015	8	72+
(5)			870	700	14	1.3	18	1110	..	..

Entered with an unimportant family and previous history. Eight days before admission he complained of redness, heat and swelling in his left ankle, which ascended to the knee. On physical examination the heart was negative save for a systolic bruit transmitted from apex to axilla. Otherwise physical examination was negative except for the joint condition. The patient ran a protracted course of irregular fever, developing fluid or pus in various joints. The spleen became palpable, obscure signs in the chest and abdomen occurred. During observation the blood-pressure steadily rose, albumin appeared in the urine, with many casts. Clinically amyloid nephritis was suggested.

The kidneys showed normal function save that the lactose was not entirely excreted within twelve hours, while the phthalein was on the lower border of normal (55 per cent. for two hours), findings which suggested either a very mild nephritis or chronic passive congestion without nephritis.

The autopsy (No. 3,713) three months later was especially interesting. There was a large retroperitoneal abscess walled off by a mass of chronic inflammatory tissue in which the capsules of the kidneys were imbedded. The kidneys were of normal size, and grossly did not appear remarkable. Microscopically, however, they showed well-marked congestion of capillaries without evidence of acute or

chronic nephritis. It is suggested that the functional picture obtained was due to congestion caused by pressure from the abscess. There is no positive proof. The functional results, however, are identical with those obtained experimentally in mild passive congestion.

No. 82,004. Tailor, 42 years old.

Family and previous history were negative save for small-pox and acute articular rheumatism in youth. He had passed "renal calculi."

One week before entry he was suddenly seized with pain in the right flank, coming in attacks for variable lengths of time, radiating to the hypogastrium, and so severe as to require morphin.

Physical examination showed a man slightly cyanosed and dyspneic. His heart was not enlarged, but the aortic second sound was ringing. The lungs were negative, the abdomen was negative save for slight tenderness in the region of the right kidney. The blood-pressure at entry was 160, but rapidly fell to 130. The

MISCELLANEOUS CASES

Phthalein		Urinalysis			Nitrogen in Blood	Urea in Blood	Remarks
1 Hr.	2 Hrs.	Alb.	Blood	Casts			
..	38	+	0	+	700	...	Casts and albumin disappeared under treatment. Patient left hospital improved.
..	60	..	..	..	...	...	
50	55	+	0	+	...	...	Patient died without symptoms of uremia. Autopsy No. 3713. Chronic passive congestion.
..	..	..	..	..	...	...	
12	28	+	0	0	600	200	Urine cleared up after passage of stone. Patient left hospital improved.
..	..	..	..	..	...	...	
20	..	0	0	0	308	280	Second phthalein test two weeks later. Patient left hospital improved.
55	70	..	..	..	...	...	
13	23	+	0	0	...	...	Lactose intramuscularly. Bence-Jones albumosuria. Patient died without symptoms of uremia. No autopsy.
..	..	..	..	..	..	...	

urine showed a specific gravity of 1,020, a trace of albumin, some red blood corpuscles and leukocytes but no casts. On the day of discharge a freshly passed specimen showed no albumin, blood or casts.

The functional tests showed the patient unable to excrete salt and having a low phthalein output (28 per cent. for two hours). Lactose and iodid excretions were normal. The patient passed calculi, but refused to remain in the hospital longer. The decreased renal function in this case was probably due to the injury from renal calculi. It is impossible to decide from the limited study of the case whether in addition there was a co-existent chronic nephritis, but the findings seem of sufficient interest to be reported in detail.

No. 81,925. Steward, 32 years old.

Entered for the third time. His family and previous history were negative. He had entered the hospital seven years previously with the same history as at present, viz.: "Hemorrhage from the bowels and weakness." His previous diagnoses were variable. It seems probable that the patient had either Banti's disease or a tuberculous polyserositis. Physical examination suggested an adherent pericardium; there was an enlarged liver and spleen with ascites. There was slight edema of legs. The patient was markedly anemic; 26 per cent. hemoglobin, 2,300,000 red cells.

When first tested for renal function the patient was unable to excrete salt well; the phthalein was 20 per cent. for two hours. Lactose and iodid were normal. A phthalein test repeated two weeks later showed 55 per cent. for one hour and 70 per cent. for two. It seems possible that salt excretion may have been disturbed in this case by extra-renal factors. The low phthalein in excretion may in part have been due to anemia, as at the second reading his blood condition had improved—Hgb. now 55 per cent. and 4,000,000 R. B. C. Considering the later test and other results, the impression is that the patient had no nephritis.

No. 82,971. Housewife, 35 years old.[35]

The patient's father died of "cancer." She had always been well until six months before entry, when she noticed pain in her right hip. Two months later her left hip became tender, a month later she noticed a small mass in her right breast which grew rapidly in size.

In the last few weeks she had grown very weak; since her illness began she had lost 40 pounds in weight.

Her physical examination was negative save for a tumor of the right breast with involvement of sacrum, iliac bones, femur and fibulae. There was a suggestion of involvement of the frontal bone and spine. The urine contained Bence-Jones protein but no blood or casts. Tests of renal function showed that the patient was unable to concentrate salt or to excrete it through diuresis, to excrete iodid or phthalein normally, while her lactose was slightly delayed. The functional results here suggested more than any others obtained a tubular nephritis with tubular hyposthenuria. The patient died, but there was no autopsy permitted; therefore the significance of these findings can not be determined.

On the whole, this group is of interest as illustrating certain atypical findings. It is difficult to interpret the cases and results more thoroughly.

GENERAL SUMMARY

Our studies permit of the following summary and deductions:

1. In the group of cases studied the quantity of urine has been variable. There has been no constant relationship between the existence of polyuria or oliguria and the condition of the patient as determined by other functional studies or clinical observation.

In cases with cardiac involvement the amount of urine has been exceedingly variable, apparently depending on the degree of myocardial insufficiency, edema or other extra-renal influences. Hence, the quantity of urine was of little value in determining the condition of renal function.

2. The specific gravity of the urine in the most advanced cases of nephritis has been constantly low; in other cases variable. In general, cases with cardiac decompensation have shown a urine of higher specific gravity than those with pure nephritis, and cases of advanced nephritis with cardiac insufficiency have shown a less concentrated urine than cases of cardiac insufficiency with little nephritis.

3. Sodium chlorid added to the diet in considerable amounts has been excreted normally in the majority of cases studied. In advanced nephritis it has been excreted in amounts less than those ingested. In neph-

35. Reported by Drs. Boggs and Guthrie, Bull. Johns Hopkins Hosp., December, 1912.

ritis with cardiac decompensation its excretion has varied, certain cases retaining it — whether or not complicated by edema — others of more advanced nephritis clinically and functionally, excreting more than ingested.

Moreover, these studies have suggested that patients who have been on a salt-poor diet for any considerable length of time, are unable to excrete added amounts readily, irrespective of the cardio-renal condition. Therefore, the study of salt excretion alone, as a test for renal function, is of little value. Its value consists in affording corroborative evidence to other tests, but owing to the many extra-renal factors to which it is subjected, its absolute value is slight.

4. Lactose excretion has been delayed in all cases of nephritis or chronic passive congestion. Cases in which no lactose has been recovered in the urine within twelve hours after injection were clinically instances of severe nephritis. Although the failure of lactose to appear in the urine is of considerable value prognostically, we do not feel that the number of hours necessary for complete elimination is a valuable index of the renal condition.

As already indicated, the mechanism of its excretion is not determined, although it must differ essentially from that of iodid, salt or phthalein. A marked delay in its excretion suggests a disturbance of renal function which may be manifested in no other way. Its exact significance is unknown.

5. The potassium iodid excretion has varied markedly. In the cases of most marked nephritis it has been delayed. In cases of congestion clinically suggesting but little nephritic involvement, it has also been delayed. In one case clinically of advanced nephritis (confirmed by autopsy) it has been normal. There seems to be no constant relationship between the degree of nephritis or of congestion and the excretion of the drug. Hence its time of excretion as a test for renal function is practically worthless.

6. Phthalein has been excreted in amounts paralleling the degree of functional involvement of the kidney, as indicated by the clinical condition, subsequent history, or autopsy. In marked chronic passive congestion without nephritis it has been low at first, but has returned rapidly to normal with improvement of circulation. In cases of chronic passive congestion with nephritis its excretion has remained persistently low, apparently indicating the actual functional capacity of the kidney.

Therefore, the phthalein test for renal function has afforded the most reliable information as to renal efficiency and has been of great value in differentiating functional incapacity due to nephritis from that due to chronic passive congestion.

7. The marked accumulation of incoagulable nitrogen in the blood when present is valuable evidence of renal insufficiency. How great the value of this test is we are unable to state from our own experience.

Our cases which correspond to those studied by Schlayer are considered in Groups II and III. The first are of "vascular nephritis" predominantly. This is evidenced by a delayed lactose excretion accompanied in one case by "vascular hyposthenuria" and diuresis. Tubular function was normal as indicated by the ability to concentrate salt and by a normal iodid excretion.

The cases of Group III would fall into either his groups of "tubulovascular" or "vasculo-tubular" nephritis. Lactose excretion is delayed, in many instances there is hyposthenuria of a mixed type. The tubes are involved as shown by their inability to concentrate salt and in certain cases by a delay in the iodid excretion.

The chief importance in studying cases in this way is the ability afforded to recognize as early as possible abnormalities in renal function, and by repeating these tests over intervals of time to follow the subsequent course of the disease in any individual patient. For practical purposes it seems from these studies that in advanced nephritis the phthalein and incoagulable nitrogen tests give more definite and reliable information prognostically than the others used; in early cases or suspected cases, the lactose, iodid and salt tests may prove of value.

CONCLUSIONS

1. *The functional condition of the kidney can unquestionably be determined much more accurately by the use of these tests than through ordinary clinical studies alone.*

2. The phthalein test is of great diagnostic and prognostic value. For general use it is of more value prognostically than any other single test; diagnostically, also, it is of value in cardiorenal disease for determining the relative responsibility of the heart or kidney for the clinical condition.

The lactose test is of great value diagnostically in determining the existence of abnormal renal function. The significance of its delayed excretion is obscure. The suppression of the excretion of lactose may be of considerable value prognostically.

The salt test if considered alone is of no value, since it is subjected to so many extra-renal factors. When considered in conjunction with clinical and other functional studies, it may prove of some value diagnostically and prognostically.

The amount of water excreted in cases of pure nephritis in response to sodium chlorid stimulation may be of diagnostic value.

The potassium iodid test is of little value diagnostically or prognostically.

The marked accumulation in the blood of incoagulable nitrogen, in cases of nephritis when present, is of considerable prognostic value.

3. It is possible in cases of cardiorenal disease with varying degrees of chronic passive congestion and nephritis to determine which factor is of greater importance in the causation of the clinical picture encountered. This can be done most readily by repeated phthalein tests, while the determination of incoagulable nitrogen in the blood may also be of value. The lactose and iodid tests are of no value in this respect.

4. It is possible by these tests to diagnosticate the presence or absence of impairment of renal function in cases in which clinically nephritis is suggested. In this respect the lactose and phthalein tests are of most value.

5. Before feeling convinced of the justifiability of drawing conclusions relative to the involvement of the vascular or tubular functions under pathological conditions, we feel that a much deeper knowledge concerning the physiology of the excretion of these various substances studied is necessary.

It is with the greatest pleasure that we acknowledge our indebtedness to Dr. Barker, Dr. Thayer, and the other members of the medical staff of the Johns Hopkins Hospital for their cooperation and interest in this work. To Dr. Thayer we are particularly grateful for many helpful suggestions and for clinical material.

EXPERIMENTAL OBSERVATIONS ON THE EFFECTS OF THE ADMINISTRATION OF IODIN IN THREE CASES OF THYROID CARCINOMA (TWO HUMAN AND ONE CANINE)*

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There is no doubt that in the development of normal tissues structural differentiation and functional differentiation parallel each other, but in the case of tumors little is known as to whether any such parallelism exists. One obvious reason for this is that very few of the tissues from which tumors most frequently develop have any readily estimated physiological attributes. Beginnings have been made in this direction in the case of adrenal tumors (hypernephromas) through investigations for the presence of the specific pressor substance.[1] So also considerable work has been done with lipomas by way of chemical analysis and comparison with the fat of normal adipose tissues.[2] For investigations in this field it has long seemed to us that the thyroid offered most favorable conditions. Thus its architecture is simple; it is localized, easily accessible and has a wide range of morphological variations within the limits of normal functional activity. In man it is one of the most frequent sites for tumor development, particularly the adenomas. The most favorable factor, however, is that the easily determined iodin offers a fair test for the functional activity of this tissue. Thus it is well known that iodin to a marked degree controls the morphological changes associated with the physiological variations and overgrowths in the gland and also that iodin is an essential constituent of the active principle of the gland's secretion. It is on the basis of a rather extensive experience with the relation of the iodin content to gland structure and on the comparative effects of iodin on the thyroid in various phases of physiological activity that some years ago one of us undertook the study of the relation of the iodin content of benign epithelial tumors (adenomas) to their histological structure and of the effect of the administration of iodin on such tumors in comparison with its effects on the adjacent non-tumor thyroid. Some of these observations have been published.[3] Summarizing briefly it was

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1. Brooks: Jour. Exper. Med., 1911, xiv, 550.
2. Wells: THE ARCHIVES INT. MED., 1912, x, 297.
3. Marine: Jour. Med. Research, 1913, xxvii, 228.

found that all benign epithelial tumors have some capacity for iodin, but that this is always much below that of the adjacent non-tumor thyroid. There are variations in the capacity of these tumors for iodin which in a general way run parallel with the degree of morphologic differentiation. Thus simple adenomas or the most differentiated group have the greatest capacity, approaching closely in some instances to that of the non-tumor thyroid tissues, while the fetal adenomas, or the least differentiated have the least capacity for iodin. In the interpretation of these findings it was suggested that benign epithelial tumors of the thyroid are only partial tumors, in that they still have preserved, to some degree at least, one easily detectable, physiological attribute of the non-tumor thyroid tissue.

In view, therefore, of the well-known iodin relations in the simple non-tumor functional hyperplasias (goiter) and of the findings in the benign epithelial tumors, it seemed of importance to extend these observations to include malignant epithelial hyperplasias of the thyroid. During the past year two opportunities for such observations in man have occurred, and it is through the courtesy of Drs. C. A. Hamann and E. P. Carter, in whose services at the City Hospital the cases were admitted, that we have been able to observe and follow them to their termination. In both cases a portion of the thyroid tumor was removed several months before death, iodin was administered for a long period of time and autopsies were obtained. Abstracts of the cases follow:

ABSTRACTS OF CASES

CASE 1.—J. K., City Hospital No. 11766, admitted November 2, 1911. Male, Pole, aged 37, laborer. Owing to poor interpretation only a partial history was obtained.

Complaint: Enlargement of the neck with pain.

Physical Examination.—Patient was well developed and fairly well nourished. There was slight bilateral prominence of the eyes, no tremor, no tachycardia. General glandular enlargement with an increase in the size of the thyroid involving both lobes and the isthmus. The thyroid was somewhat tender on pressure and on deep palpation was slightly nodular. Admission temperature 102.3 F., pulse 80, respiration 18. Thyroiditis was suspected. Blood Examination: Hgb. 85 per cent.; R. B. C. 4,200,000; W. B. C. 8,600. Differential count: Polymorphs. 67 per cent.; mononuclears 10 per cent.; lymphocytes 17 per cent.; eosinophils 1 per cent.; transitionals 5 per cent. Urine on November 16 showed a trace of albumin.

November 5, 1911, measurement of neck in largest circumference 42 cm.

November 12, 1911, measurement of neck in largest circumference 40 cm. Temperature 98 F., pulse 90, respiration 20. The thyroid at this time was distinctly nodular and apparently adherent to adjacent structures. A small nodule was made out just above the clavicle on the left side. Malignancy was suspected at this time.

Nov. 14, 1911. Syrup of ferrous iodid was begun in doses of 8 minims t. i. d. The condition of the patient remained but little changed until November 25 when Dr. Hamann removed the left lobe, isthmus and part of the right lobe.

Pathological Report.—Right lobe and isthmial portion: The mass is hard, slightly nodular and covered with numerous tags of tissue from the separation of fibrous adhesions. It has neither the shape nor the general appearance of thyroid. Weight of mass 76 grams. On section the surface nodules are found to be adenomatous masses five in number, the largest measuring 3 by 3 cm. One contains calcareous deposits, another is cystic, and the smaller ones are glandular throughout. These adenomas are imbedded in a hard, white scar tissue throughout which are yellowish, necrotic areas varying in size from 1 mm to 6-8 mm. These areas resemble the caseation seen in certain types of tuberculosis or actinomycosis. No true thyroid parenchyma is made out. The general appearance is that of a chronic inflammatory process in a pre-existing adenomatous goiter.

Microscopic Examination.—Sections from seven areas of the tumor mass were studied. In only one was there evidence of non-tumor thyroid tissue and this was very sclerotic, with small, shrunken follicles. Sections through two of the adenomas revealed characteristic adenomatous structure composed of small, uniform, closely-set colloid-containing follicles in the subcapsular zone with atrophy and hyaline degeneration of the central portion. The non-adenomatous tissue is for the most part dense, infiltrated fibrous tissue with scattered islands of tumor cells occupying clefts and quite frequently filling the lumina or veins. These tumor areas correspond to the necrotic yellowish areas noted in the gross specimen. The cells are uniformly distributed throughout a given tumor area with no differentiation into follicle formations. The cells are highly irregular in size. Their nuclei are irregular in size and staining intensity, resembling sarcoma as much as carcinoma. Hemorrhage and necrosis are present in all the larger areas. In a few of the areas suggestive follicle formations are present owing to the presence of very scant stroma. On this account the possibility of the tumor being one of those rare, sarcocarcinomas comparable to those described by Wells[4] in the dog, by Leo Loeb[5] in the rat, and Woolley[6] in man, was considered. Almost all of the described cases of this double tumor have been primary thyroid tumors. A study of the metastases in our case eliminates this possibility.

Dec. 1, 1911. Wound healing, back rest, temperature 98 to 99 F., pulse 90 to 100, respiration 18 to 20.

Dec. 8, 1911. Sodium iodid grs. 3 t. i. d. substituted for the syrup of ferrous iodid. Wound healed, temperature normal, pulse 80 to 90, respirations 20.

Dec. 18, 1911. Patient complains of pain in the right thigh and knee. A small mass on the inner side of the right ilium was made out. *X*-ray plates at this time were negative.

Dec. 23, 1911. Patient's general condition fair. Was discharged.

Jan. 2, 1912. Patient re-admitted complaining of pain in the region of the eighth rib in the right axillary line and in the right hip. Physical examination shows no noteworthy change in the neck region. There is a small palpable tumor mass attached to the eighth rib in the axillary line and a tender mass in the right inguinal region. The face had a sallow, puffy appearance. There is increased dulness over the manubrium. The superficial veins of the thorax and abdomen are becoming prominent and somewhat tortuous. An *x*-ray plate taken at this time shows mediastinal growth extending to the left and to the right of the base of the heart; also a mass in the left ninth rib posteriorly.

Jan. 11, 1912. Complains of pain in the right inguinal region and in the right arm. The face is cyanotic and edematous; veins of the neck very much distended.

Jan. 15, 1912. Patient is quite ill; face greatly enlarged and cyanotic. The temporal veins are much distended. Motor power on the right side is decreased. Reflexes diminished. Right arm swollen.

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4. Wells, H. C.: Jour. Pathol. and Bacteriol., 1901, vii, 357.
5. Loeb, Leo: Am. Jour. Med. Sc., 1903, N. S. cxxv, 243.
6. Woolley, P. C.: Am. Med., 1902, iv, 331.

Jan. 16, 1912. Tongue enlarged. Speech and swallowing difficult. Morphin grs. ¼ two to three times per day necessary to control pain.

Feb. 24, 1912. The mass in the right inguinal region had progressively enlarged. Superficial veins of the abdomen and thorax have undergone further enlargement and edema of the face, tongue and neck region is very much lessened.

March 16, 1912. Patient had lost much weight, most marked pain now is in the thorax. Well developed collateral circulation around the obstructed superior vena cava.

April 9, 1912. Obstinate constipation, great emaciation, continuous pain, anxious pinched appearance, catheterization necessary.

April 19, 1912. Patient died this morning. Autopsy three hours later.

Autopsy Report.—Body length 170 cm. Marked emaciation; rigor mortis present.

Old thyroidectomy wound. The laryngeal cartilages and neck muscles are obscured by diffuse subcutaneous thickening. There is marked tortuosity of the veins of the chest and abdomen. A large rounded mass about 12 cm. in diameter in the right iliac fossa. The right leg muscles are distinctly atrophic.

Internal: On removing the sternum the tumor mass was found to involve the manubrium and both clavicles. No excess of fluid in the pleural cavities. The thymus area is replaced by tumor tissue which is continuous with the thyroid area above. Right lung free from adhesions and air-containing. Many nodules varying from 1 to 5 cm. in diameter are scattered throughout the lung. No consolidation. Bronchi reddened and contain some mucopurulent exudate. Left Lung: Few adhesions at apex and near the base, air-containing. Multiple tumor nodules of approximately the same size and distribution as in the right lung. These tumor nodules are grayish opaque in color. Many of the masses have central areas of necrosis. In the eighth rib on the right side there is a fusiform swelling which on section proved to be a medullary metastasis. On the left side springing from the ninth rib is a hemispherical mass 4 by 5 cm. in diameter projecting into the pleural cavity but completely covered with pleura.

Heart: Pericardial surfaces smooth. There is no excess of fluid. Heart muscle soft and flabby. The superior cava is completely blocked by tumor growth, distending the vessel to a diameter of 2 to 2.5 cm. and extending up into the innominates and down into the right auricle. Pulmonary veins, inferior cava, aorta, and pulmonary artery free. Liver: Normal appearance, free from metastasis. Spleen: Slightly enlarged. Malpighian bodies and trabeculae prominent. Kidneys: Right measures 11 by 6.5 by 4.5 cm. Capsule strips readily. On the surface are many yellowish raised spots distributed over the entire cortex. On section the surface spots extend through the cortex as yellow streaks. Left kidney similar in all respects to the right. Adrenals normal. Pancreas normal. There is a small metastasis in the mesentery of the transverse colon. Occupying the right iliac fossa and elevating the iliacus muscle and crural nerves, also extending downward into the pelvis and involving the rectum, is a large mass about 15 cm. in diameter. The mass extends through the ilium, involved the ischium at the acetabulum, and also the right side of the sacrum. On section the tumor tissue is soft, grayish, hemorrhagic, with extensive areas of necrosis. There is a separate metastasis in the body of the fifth lumbar vertebra. The thyroid area was removed with the tongue. The left lobe and isthmus are operatively absent. The entire area was now filled with scar tissue and tumor growth. The right lobe area contains a tumor mass in which no distinct thyroid tissue is visible. The esophagus is free save for very prominent varices in the upper and lower thirds. Several small tumor masses project into the lumen of the trachea between the cricoid cartilage and the bifurcation.

Microscopic Examination.—Pancreas and liver normal. Spleen: Malpighian bodies and pulp cells well preserved. Kidney: No increase in connective tissue. Throughout the cortex are irregular areas of cellular exudate composed for the most part of polymorphonuclear leukocytes. In some of the areas the tubules

remained visible while in others actual abscess formation has taken place. Throughout all the acute inflammatory areas the tubules contain pus cells. Diagnosis: Acute suppurative nephritis. Heart muscle normal. Lung: Congested; moderate coal pigmentation; free from inflammatory exudate.

Thyroid Area—Right Lobe: Four sections. No trace of thyroid tissue visible. Extensive areas of tumor cells in the dense stroma. The tumor masses for the most part show no follicle formation. In some, however, slight differentiation but without formation of lumina can be made out. Same irregularities in the cell types as were noted in the operative specimen.

Lung Metastases: Slight encapsulation; central areas necrotic. The cortical zone is divided into small columns and strands of tumor cells by a very delicate vascular stroma. Slight evidence of follicle formation. The inguinal tumor mass also exhibits slight follicle formation. Rib metastasis: Fibrous stroma more prominent and distinct follicle formations can be made out, some of which contain colloid-like material. The tissue is distinctly thyroid in type although the cells are as atypical as in other metastases, with less evidence of follicle formation. The bronchial lymph-glands contain tumor metastases, the cells of which showed no follicle formation. Tumor from superior cava contain a delicate capillary stroma in places outlining very irregular attempts at follicle formation. The cell types are highly irregular. Nuclear figures are present.

Anatomical Diagnosis.—Adenocarcinoma of the thyroid, medullary type. Metastases into trachea, the mediastinum, bronchial lymph-glands, lungs, ribs, fifth lumbar vertebra and ilium. Acute suppurative nephritis.

Iodin determinations were made on several of the tissues and metastatic tumor nodules obtained at post-mortem as well as on the tumor mass removed at operation.

Iodin Determinations.—Operative Specimen No. 1. The scar-like tissue corresponding to the thyroid area contains 0.02 mg. per gram of dried tissue.

No. 2.—Adenoma freed from all other tissues contains 0.17 mg. per gram of dried tissue.

Autopsy Tissues:

No. 1.—Liver: Iodin per gram dried tissue, 0.00 mg., or a trace.
No. 2.—Kidney: Iodin per gram dried tissue, 0.01 mg.
No. 3.—Pancreas: Iodin per gram dried tissue, 0.03 mg.
No. 4.—Spleen: Iodin per gram dried tissue, 0.00 mg.
No. 5.—Lung: Iodin per gram dried tissue, 0.00 or a trace.
No. 6.—Lung Metastasis: Iodin per gram dried tissue, 0.00 mg.
No. 7.—Rib Metastasis: Iodin per gram dried tissue, 0.00 mg.
No. 8.—Iliac Metastasis: Iodin per gram dried tissue, 0.00 mg.
No. 9.—Tumor from the site of the right lobe: Iodin per gram of dried tissue, 0.00 mg.

Iodin Administration: Nov. 14 to Dec. 8, 1911, syrup of ferrous iodid 34 c.c. December 8 to 20, sodium iodid 12 gm. January 8 to April 15, 1912, syrup of ferrous iodid 181 c.c. Total iodin before operation, 17 c.c. syrup ferrous iodid. Total iodin after operation, 12 gm. of sodium iodid and 198 c.c. of syrup ferrous iodid.

Case 2.—S. R., City Hospital No. 11,167; admitted Sept. 11, 1911. Female, Hungarian, aged 39. Complaint, cough with loss of weight for the past ten months. Past history not obtained.

Physical Examination.—Fair development, poorly nourished and cachectic appearance. There is a unilateral tumor mass 5 cm. in diameter in the region of the left lateral lobe of the thyroid. Patient has noticed this enlargement for seven years. Right lobe slightly enlarged but with normal outline. The chest is long and the costal angle narrowed. There is distinct dulness over the right apex and bronchial breathing over both apex and base. Heart, abdomen, and extremities negative. No blood examination. Trace of albumin first noticed December 23, which continued until death. Repeated examinations of the sputum for tubercle

bacilli negative until April 30, 1912, although patient had afternoon temperature of 101 to 102.8 F. with pulse averaging 100 to 110.

Dec. 3, 1911. General condition of patient about the same as at admission. The thyroid tumor had enlarged slightly. It is quite hard and not painful. Displacement of the larynx to which the tumor mass is firmly attached. Skin movable over the tumor. Several isolated nodules are palpable in the left supraclavicular fossa. There is distinct dulness over the left apex of the lung and *x*-ray plates showed rather dense shadows in both apices.

Dec. 12, 1911. Evidence of tracheal stenosis and operation advised.

Dec. 20, 1911. The tumor mass was removed.

Pathological Report.—The mass consists of the left lobe and isthmus. It is firm, nodular, and for the most part encapsulated but in places the tumor tissue extends through. Two of the superficial veins are filled with tumor tissue. On section the tumor mass is whitish, opaque, with a few small necrotic areas. The tumor is sharply defined from the non-tumor thyroid tissue which has all the appearances of normal thyroid tissue. Coarse fibrous strands cut the tumor mass into lobules. In places colloid-like substance is seen.

Microscopic Examination.—The non-tumor thyroid tissue is uniformly colloid-containing, slightly stretched by the growing tumor but in all respects resembles pure colloid thyroid. The tumor is for the most part undifferentiated into follicles. The interior portion is composed of irregular columns of large cuboidal cells closely set and for the most part without evidence of lumina. There are areas throughout this portion of the tumor in which irregular follicle formations occur. In the peripheral parts of the tumor follicle formation is absent. There is a distinct alveolar arrangement dependent on the stroma. The tumor cells are somewhat irregular, elongated, and with their long axes arranged radially in the alveolus. No adenoma-like areas were made out. Diagnosis, medullary carcinomas.

Dec. 24, 1911. Recovery from operation uncomplicated. Temperature 99 to 101 F.; pulse 110 to 115. Sodium iodid grains 5, daily. Patient complains of pain in the right hip.

Jan. 10, 1912. Cachexia and emaciation not improved, breathing is better. The right leg is swollen and somewhat painful. *X*-ray at this time shows metastases in the right side of the sacrum.

Feb. 27, 1912. Syrup of ferrous iodid minims 10 t. i. d. was substituted for sodium iodid. Flatness over the right chest and the infraclavicular region of the left with dulness beneath the manubrium. No recurrent growth in the thyroid region.

March 20, 1912. Patient's condition progressively downward. Respiration 24 to 28, pulse 110 to 113; temperature 99 to 100. Constant pain in the sacro-iliac region.

April 30, 1912. Sputum contains tubercle bacilli. Transferred to tuberculosis sanitarium and died there May 3, 1912.

Autopsy.—Autopsy May 5, 1912, after overcoming some difficulties. The body was not embalmed and was in a good state of preservation. Slight discoloration of the abdomen. Examination confined to the chest and abdomen. Thyroid area: Right lobe normal shape, enlarged about twice the normal size. Firm, translucent, and on section contains abundant colloid. A cystic adenoma 2 cm. in diameter is imbedded in this lobe. The isthmus was removed at operation. The left lobe for the most part was removed. There is, however, a mass of tissue 4 by 1.5 cm. occupying the site of the left lobe, and adherent to the surrounding structures. On examination this mass is found to contain both colloid and cancerous thyroid tissue. The thymus area contains three metastatic tumor nodules, the largest being the size of a golf ball. Both lungs are adherent to the parietal pleura. The right lung contains extensive tuberculous caseation and consolidation. Both lungs contain numerous tumor nodules varying in size from a pea to a golf ball. Heart, small; contains no metastases. Abdomen: Liver contains several metastases, one

large nodular mass just above the gall-bladder, measures 6 by 5 by 5 cm. Spleen contains one small tumor nodule. Kidneys both contain metastases. Pancreas contains a metastasis 2 cm. in diameter near the duodenum. All metastases observed in the several viscera are grayish opaque in color, soft, friable, and have no gross resemblance to the normal thyroid structure. There are several metastases in the omentum and mesentery. The sacrum contains a large metastasis extending into the pelvis and also producing slight ulceration externally. Stomach and intestines appear normal.

Microscopic Examination.—Thyroid: Right lobe has all the appearances of pure colloid thyroid. The small adenoma has a subcapsular zone of well preserved, closely set small follicles most of which contain some colloid. Diagnosis: Intermediate adenoma with involutionary changes imbedded in the pure colloid goiter. Three other sections from the right lobe revealed no metastases. Examination of tissue removed from the region of the left lobe shows for the most part dense scar tissue in which are pockets of tumor tissue without any differentiation into follicles. In another section of this mass considerable non-tumor thyroid tissue similar to that of the right lobe is present. Lung metastases encapsulated. They consist of irregular branching columns of tumor cells with slight follicle formations. The cells for the most part are spindle-shaped with a tendency toward radial arrangement from the center of the column. In some of the columns lumina are made out. Liver metastases are in all respects similar to those of the lungs. Pancreas metastasis is composed of branching columns of spindle-shaped cells. Many of these columns have definite lumina. The pancreatic tissue has undergone extensive post-mortem changes. The kidney metastases have a distinct alveolar arrangement of the tumor cells with little or no tendency to form follicles. The surrounding kidney tissue including capsule, glomeruli and tubular epithelium are relatively normal.

Iodin Determination.—Operative Specimen: No. 1.—Iodin per gram of dried non-tumor thyroid, 0.80 mg.

No. 2—Iodin per gram of dried tumor thyroid, 0.03 mg.

Autopsy Tissues:

No. 1.—Right lobe, pure colloid gland, iodin per gram of dried gland, 2.92 mg.
No. 2.—Left lobe, mixed tumor and non-tumor thyroid, iodin per gram of dried gland, 0.16 mg.
No. 3.—Lung metastasis, iodin per gram of dried gland, 0.00 mg.
No. 4.—Liver metastasis, iodin per gram of dried gland, 0.00 mg.
No. 5.—Esophagus tissue, tumor-free, iodin per gram of dried tissue, 0.00 mg.
No. 6.—Pancreas tissue, tumor-free, iodin per gram of dried gland, 0.00 mg.
No. 7.—Liver tissue, tumor-free, iodin per gram of dried gland, 0.00 mg.

Administration of Iodin.—Total iodin before operation, 0.

Total iodin after operation: (a) Dec. 24, 1911, to Jan. 5, 1912, 1 gm. sodium iodid daily; total 13 gm. (b) Feb. 27, 1912, to April 25, 1912, 10 minims syrup ferrous iodid t. i. d.; total 119 c.c.

In addition to these two human cases one of us (M.) has observed a case of thyroid carcinoma in a dog, and inasmuch as the data are in all respects similar to those for the human cases it may also be included here. The following is a synopsis of the case record:

CASE 3.—Laboratory No. A-124, male Boston Bull-Terrier, aged 8 years, owned by Dr. E. P. Carter, admitted May 1, 1908.

History.—Goiter had been known clinically for over three years, with progressive enlargement. First examined dog on Oct. 9, 1907. Thyroid lobes at this time were symmetrically enlarged, compressible, distinct, movable and connected by a broad isthmial band. Diagnosis, active thyroid hyperplasia. Lugol's solution 0.1 c.c. daily was given. This treatment was continued with very slight interruptions until May 8, 1908. The dog was seen from time to time and the thyroid lobes, which at first became smaller, began to enlarge again in February, 1908. Their

outlines became less distinct. Gradually both lobes and isthmus became fused into a single mass and the entire mass became firmly adherent to the larynx. In April the thyroid mass was more distorted, firm, and immovable, and was producing dyspnea. As the dog was now losing weight and the thyroid lobes had undergone marked changes, the probability of thyroid carcinoma was suggested and operation advised. May 8, 1908, under ether anesthesia the entire left lobe was removed. It was densely adherent to the trachea, larynx, esophagus and adjacent muscles, and weighed 145 gm.

Pathological Examination.—The lobe was nodular, although everywhere encapsulated. Consistency was firm. On section there were still some very definite areas of original thyroid tissue in the colloid state, for the most part lying just beneath the capsule, but in general the entire lobe was replaced by a new growth. The tumor tissue was grayish opaque in color, containing many small hemorrhages and small areas of necrosis, together with a few cystic areas filled with a brownish cholesterin-containing fluid. It was impossible to separate the tumor from the non-tumor thyroid tissue and duplicate iodin determinations were made on the mixed tissue with results of 0.32 and 0.30 mg. per gram of dried gland.

May 11, 1908, dog doing nicely.

May 16, 1908, wound slightly infected, and as the dog had undoubted carcinoma the owner desired him chloroformed.

Autopsy.—Slight wound infection. The right lobe weighed 125 gm., was nodular, hard, gray-red, and on section was equally involved with cancer as the lebt lobe, which was removed at operation. Extension of carcinomatous tissue into the anterior mediastinum. Both lungs contained numerous metastatic nodules varying from 1 mm. to 2 cm. in diameter. They were gray-white, friable, and contained no visible colloid. The lymph-glands along the bronchi were involved. No metastases were found in the kidneys, liver, pancreas, or other viscera. As the dog had been getting iodin up to the time of operation, iodin determinations were made on the autopsy tissues as follows:

Right lobe of the thyroid contained 0.27 mg. per gram of dried gland.
Lung metastasis contained 0.11 mg. per gram of dried tissue.
Lung tissue contained 0.07 mg. per gram of dried tissue.
Liver tissue contained 0.15 mg. per gram of dried tissue.

Histological Examination.—Thyroid: The capsule was markedly thickened. Slight round-celled infiltration. There were many areas of original non-tumor thyroid containing normal colloid and normal cuboidal epithelium. The tumor tissue was in general differentiated into follicles. These were small, rounded, closely packed and resembled the fetal adenoma follicles seen in human goiter. There were other areas or irregular islands making up probably a third of the sectioned area in which little or no differentiation into follicles could be made out. The epithelium of the formed follicles was high cuboidal in type and the nuclei were large vesicular, quite regular in size and staining intensity. Lung Metastases: Six were examined, all showing some differentiation into follicles, of the same characteristics present in the thyroid lobes.

SUMMARY AND DISCUSSION

The principle data of Case 1 are: Patient was under observation 168 days—23 days before and 145 days after operative removal of part of the thyroid tumor. Metastases were without doubt present before the patient came under our observation. The thyroid contained several adenomas of the fetal type and while it is impossible to state from what portion of the thyroid the carcinoma originated, we have come to the conclusion from the tumor pattern that it probably originated from an

adenoma. The whole course of the disease was, as far as could be determined, one of uncomplicated thyroid cancer. Seventeen c.c. of syrup of ferrous iodid was given before operation and 12 gm. of sodium iodid, and 198 c.c. of the syrup of ferrous iodid were given after operation—iodin having been continuously administered from Nov. 14, 1911, to April 15, 1912, with the exception of eighteen days from Dec. 20, 1911.

Case 2 was in the hospital continuously from Sept. 11, 1911, until her death, May 3, 1912—235 days. She was admitted for and had active pulmonary tuberculosis. Thyroid carcinoma was not definitely recognized until December 3, when, owing to tracheal stenosis, a palliative operation was advised. The tuberculosis doubtless hastened death. The tumor though metastasizing was of slower growth than that of Case 1. The carcinoma and the tuberculosis were joint factors and the individual importance of each cannot be estimated. In this case also there was one typical adenoma in the right lobe and the general type of tumor led us to look on this carcinoma as also originating in an adenoma. No iodin was given prior to the operation. Following the operation iodin was given continuously until April 25, 1912—eight days before death—with the exception of fifty-two days following Jan. 5, 1912. She received a total of 13 gm. of sodium iodid and 119 c.c. of syrup of ferrous iodid.

Case 3 (a dog) was under observation for approximately seven months. Carcinoma was suspected after the fifth month. Small doses of Lugol's solution were administered by mouth with slight interruptions from October until May 8. The total amount of iodin used could not be obtained.

The scar-like mass of the left lobe removed at operation in Case 1, after freeing it from all visible adenomatous tissue, contained 0.02 mg. of iodin per gram of dried tissue. The adenoma from the same lobe contained 0.17 mg. of iodin per gram of dried tissue. The patient had been getting iodin for eleven days before operation. Adenomas of histological differentiation present in this case normally contained some iodin, and while the comparatively high content may be explained on the basis of the iodin administered, this does not seem likely, judging from our experience with adenomas in general. The iodin content of the scirrhus cancer tissue is, on the other hand, probably due to the administration of iodin, judging by the distribution of iodin in the tissues and its rate of excretion following its administration in dogs and rabbits.[7] The iodin contents of the tissues at autopsy, notwithstanding the fact that iodin was given until five days before death, shows no traces of iodin in the remaining scar-like cancerous mass of the right lobe, in the spleen, in the rib, lung, or iliac metastases. Definite traces of iodin were found in the lung and liver tissues while the kidney and pancreas con-

7. Boruttau: Ztschr. f. Exper. Path. u. Therap., 1910, viii, 418.

tained 0.01 and 0.03 mg. per gram of dried tissue, respectively. The fact that the pure cancer tissues were free from iodin while the adenomas had over eight times as much iodin as any of the other thyroid tissues and about six times as much as the pancreas, possibly suggests that this was the best preserved thyroid tissue. Certainly the carcinoma tissues showed no power whatever to retain iodin, although the tissues were exposed to the most favorable influences for iodin storage.

In Case 2 the portion of the left lobe removed at operation was separated into tumor and non-tumor tissues. The non-tumor tissue contained 0.80 mg. of iodin per gram of dried tissue, while the adjacent tumor tissue contained 0.03 mg. of iodin per gram of dried tissue. This specimen looked like pure cancer tissue, and histological examination of several areas of it showed only tumor tissue. No iodin had been administered for nearly three and a half months. The remaining portion of the left lobe obtained at autopsy contained both tumor and non-tumor thyroid tissue, but was so intermingled that no separation was possible. The mixed specimen contained 0.16 mg. of iodin per gram of dried tissue. The right lobe, which on gross and histological examination was pure colloid thyroid, contained 2.92 mg. of iodin per gram of dried gland, or nearly four times the iodin content of the non-tumor thyroid of the left lobe obtained at operation before iodin was given. In this case neither the metastases in the liver and lung nor the non-tumor liver, kidney, pancreas, lung and esophagus tissues contained any trace of iodin although iodin had been given for a long time and up to eight days before death. This case has the advantage over Case 1 in possessing an abundance of thyroid tissue unaffected by tumor, and it is noted that this tissue reacts with iodin in the characteristically normal physiological manner.

In Case 3 duplicate determinations on the operative specimen showed 0.32 and 0.30 mg. of iodin per gram of dried tissue, respectively. The examined specimens were mixed tumor and non-tumor as the tumor growth had so infiltrated the whole lobe that separation was impossible. The observation is therefore useless so far as determining whether the tumor tissue contained iodin. Likewise, the left lobe removed at autopsy was so infiltrated with cancer that separation was impossible and the iodin determination on a mixed specimen give 0.27. The lung metastases showed 0.11 mg. of iodin per gram of dried tissue, while the tumor-free lung and liver—the only other tissues examined—gave 0.07 and 0.15 mg. of iodin per gram of dried tissue, respectively. From these findings and from the general distribution of iodin in the body following its administration it is probable that all the tissues contained iodin. The fact that the iodin content of the liver was higher than that of the lung metastasis renders the iodin content of the lung metastasis of no physio-

logical significance, and the iodin content of the lung and liver is probably due to the non-excretion of the recently administered iodin. Whether iodin in the form of Lugol's solution is held by the tissues longer than iodin given as syrup of ferrous iodid is a question barely suggested by the striking difference in the iodin contents between the two human cases and the dog. In most of the work on the retention of iodin in the tissues potassium and sodium iodid have been used, the last traces of which are known to be excreted slowly. The administration of iodin in these three cases had neither a detectable inhibiting influence nor a detectable accelerating influence on the rate of growth.

In these three cases, therefore, it seems that cancer tissue exhibits practically no capacity for iodin retention, contrasted with the non-tumor thyroid, which has a marked capacity for storing iodin; and with benign epithelial tumors (adenomas), all of which in some phase of their existence have some capacity for iodin, thyroid cancer exhibits the least—in our three cases probably no capacity for iodin. We have been able to find but two incomplete reports in the literature of iodin determinations in metastatic thyroid carcinoma. Ewald[8] reported one case in which the examination of the primary tumor (a thyroid adenoma) showed no iodin, while metastases in the lung and lymph-glands showed appreciable amounts. No other details of the case are given. He suggested that further examinations should be made, since if Baumann's observations and conclusions should be established the iodin contents of tumors might afford evidence as to tumor function. Gierke[9] observed a vertebral tumor with thyroid-like structure which contained approximately 0.25 mg. of iodin per gram of dried tissue. No other details are given and on this account it is impossible to make comparisons with our tumor cases. As there are more differentiated types of thyroid carcinoma, or possibly more correctly stated, there are metastatic thyroid growths especially in bone which morphologically closely resemble fully differentiated thyroid tissue, the need of more extended observations is obvious, as it might be possible to determine through their iodin function what relation they bear to tumors, since morphology is of little value. As dogs are not known to have adenomas we suppose that the carcinoma in Case 3 arose from tissue that had undergone physiological differentiation. If such was the case the physiological attributes have been lost, as the tumor behaved towards iodin in a similar manner to the two human carcinomas. We have as yet no direct evidence that thyroid tumors, whether benign or malignant, may compensate for the function of the non-tumor thyroid. Experimental approach has so far been impossible because none of the

8. Ewald: Ueber den Jodgehalt des Adenocarcinome der Schilddrüse und seine Metastasen. Wien. klin. Wchnschr., 1896, lx, 186.

9. Gierke: Ueber den Jodgehalt von Knochentumoren mit Schilddrüsenbau. Beitr. z. chem. Physiol. u. Path., 1903, iii, 286.

lower mammals is known to have true adenomas. The often quoted observation of von Eiselsberg[10] to the effect that following the removal of a large goiter tetany developed which cleared up as sternal thyroid metastases developed, was made at a time when parathyroid and thyroid functions were not clearly separated. Such symptoms are not now believed to have connection with thyroid. More applicable are the observations of Gulliver[11] where a woman 44 years old with symptoms of myxedema dating back four years developed thyroid carcinoma with metastases, but without any noteworthy amelioration of the myxedema symptoms. This author also cites an observation reported by Hilton Fagge where a sporadic cretin with a large goiter developed thyroid carcinoma without any improvement in the cretinoid condition. Such clinical observations though meager are in harmony with the experimental chemical evidence of the cases here reported, viz., that in thyroid carcinoma there is no evidence that useful function is preserved, but rather that in becoming malignant the tissue loses most of its physiological attributes. So far as observations have extended, it would appear that benign epithelial tumors occupy an intermediate position as regards evidence of function between fully differentiated thyroid tissue on the one hand and malignant epithelium tumors on the other.

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10. Von Eiselsberg: Arch. f. klin. Chir., 1894, xlviii, 489.
11. Gulliver: Malignant Disease of the Thyroid Developing in a Case of Myxedema. Tr. Path. Soc., London 1886, xxxvii, 511.

CONCERNING THE PRESENCE OF HEMOLYSINS IN STOOL EXTRACTS*

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The following experiments were undertaken with the aim of ascertaining, if possible, whether extracts of stools from cases of essential progressive pernicious anemia contain hemolysing substances not found in normal stools, nor in stools from other diseases. If repeatedly present, this could be regarded as of some use as a further step in the clinical diagnosis of a disease the etiology of which is still uncertain and the classification of which is hardly satisfactory.

In reviewing the literature on hemolysins in the gastro-intestinal tract, I find that while much has been done with tumor and organ extracts, little attention has been paid to the stools.

Korschun and Morganroth,[1] in their work on the hemolytic action of organ extracts, describe a hemolysin thus derived, which is active against the blood-cells of the same species and possesses the following characteristics: coctostabile, soluble in alcohol, not complex, and inactive in causing antibody formation.

Later Külbs,[2] in a series of experiments on stool filtrates, showed the presence of hemolysins in cases of intercurrent and chronic intestinal disorders as well as in progressive pernicious anemia. In chronic nephritis and diabetes agglutinins were frequently encountered. The hemolytic action of the filtrates was not affected by type of diet, heating or age of filtrate, nor did the reaction play any part in the result. He found no relation existing between the indoxyl content of the urine and the hemolytic effect of the stool. The solubility of the stool and apparent quick passage through the bowel seemed to be more important factors. Thin stools taken directly from cecum and ileum were very hemolytic. He does not refer to the chemical constituents. Injections into animals of 2 to 6 c.c. produced no anemia.

In the following year Tallqvist[3] reported his results on the study of the blood changes produced by the *Bothriocephalus latus*, results which

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1. Korschun and Morgenroth: Berl. klin. Wchnschr., 1902, p. 870.
2. Külbs: Arch. f. exper. Path. u. Pharm., 1906, No. 55, p. 73.
3. Tallqvist: Ztschr. f. klin. Med., 1907, No. 61.

were most striking and of material value in explaining the etiology of such anemias. He demonstrated the presence of a lipoid substance in the proglottides of the worm, which was extremely hemolytic, could not be dissected out, formed no antibodies, was coctostabile, resistant to proteolytic ferments and showed a great affinity for red blood-cells. On subcutaneous injections into animals a definite anemia was produced, the autopsy findings being similar to those of a progressive pernicious anemia.

He refers to substances possessing similar hemolysing qualities in normal organ extracts, especially in mucous membranes of certain sections of the gastro-intestinal tract. He suggests that in many cryptogenic forms of progressive pernicious anemia there may be qualitative or quantitative anomalies in fat metabolism calling forth a pathological separation and a consequent hemolytic lipoid substance. Such substances have been described in various tumors and secretions. Thus Kullmann[4] found them in mammary and uterine carcinomata. Grafe and Röhmer[5] (whose work was later partially confirmed by Fabian[6]), in a series of over 100 cases, demonstrated hemolyzing lipoids repeatedly in the gastric contents of gastric carcinoma, while Neuberg and Reicher[7] showed that normal neutralized gastric contents of dogs were hemolytic to cells of the same animal. Later Bloch[8] claimed that if the enterogenous theory of progressive pernicious anemia was correct, the toxic agent should be found in the stools. He found hemolytic substances in the stools of six cases of progressive pernicious anemia, in chronic enteritis, (one case), and in tabes, but the most marked hemolysis occurred with normal stools. He concluded that the normally formed lipoid in the intestinal contents was rendered inert by cholesterol, and, when this failed, hemolysis occurred. The fact, however, of the strongest hemolysis having occurred in normal stools, in his own experiments, does not satisfactorily support this theory. He used alcoholic and ethereal extracts only. The substance was not activated by lecithin. Wohlgemuth found hemolysins in pancreatic juice, which were activated by lecithin.

Next Faust and Tallqvist,[9] after further studies in the chemistry of *Bothriocephalus* proglottides showed the lipoid substance to be soluble in warm alcohol and ether, but not in water, and only capable of producing hemolysis when the sheath was disintegrated. The fatty material contained phosphorus from lecithin. Cholesterol was crystallized out, but was not hemolytic. Free fatty acids were found to be intensely hemo-

4. Kullmann: Berl. klin. Wchnschr., 1904, No. 8.
5. Grafe and Röhmer, D.: Arch. f. klin. Med., 1908, No. 93, p. 159.
6. Fabian, D.: Arch. f. klin. Med., 1908
7. Neuberg and Reicher: Biochem. Ztschr., 1907, No. 4, p. 28.
8. Bloch: Biochem. Ztschr., 1908, No. 9, p. 498.
9. Faust and Tallqvist: Arch. f. exper. Path. u. Pharm., 1907, No. 57, p. 367.

lytic, but on further analysis palmitic and stearic acids (saturated) produced no hemolysis, while the unsaturated oleic acid was intensely active. When in combination with a cholesterin ester, it was most effective, although the cholesterin ester of fatty acids is present in most normal blood-serum in small amounts.

Cholesterol in feces is in part enterogenous, while part comes from bile and some from soap in chyle. Faust and Tallqvist hold that stimulation of the intestinal mucous membrane leads to a greater formation and secretion of this substance, and, with it, an increase of soap in chyle and in blood. Thus, through abnormal stimulation of a normal process, blood destruction could be produced.

By feeding *Bothriocephalus* lipoid to dogs large amounts of very hemolytic chyle were recovered in a few hours. Chyle showed neutral fat and free fatty acids, the latter being intensely hemolytic, due to oleic acid. No cholesterol was found in chyle.

Goodman and Robinson,[10] in an unpublished work, demonstrated the presence of hemolytic lipoid substances in ethereal extracts of stools from anemias and uterine carcinoma as well as in normal stools.

TECHNIC

To weighed stool an equal volume of .85 per cent. NaCl was added, the mixture ground up in a mortar, filtered through gauze and allowed to extract over night in an ice-chest. On the following day the mixture was shaken, centrifuged and the supernatant fluid passed through a Berkefeld filter, the filtrate being used as the extract, 1 c.c. representing 1 unit. To a series of tubes containing 1 c.c. of a 5 per cent. emulsion of washed red blood cells from the patient whose stool was being examined, was added a varying amount of the stool extract, from 2 c.c. down to .1 c.c. Sufficient physiological salt solution was added so that the mixture in each tube was brought up to 3 c.c. Similar amounts of the stool extract were added to a 5 per cent. emulsion of foreign human washed red blood-cells. The protocol is as follows:

PROTOCOL OF EXPERIMENT WITH STOOL EXTRACT

Diagnosis	Amount of Stool Extr. 1 c.c.=1 Unit c.c.	5 Per cent. Emulsion R.B.C. of Same Case, c.c.	5 Per cent. Emulsion Foreign R.B.C. of Normal Resistance, c.c.	Hemolysis
.....	2.0	1	—	.....
.....	1.0	1	—	.....
.....	0.5	1	—	.....
.....	0.1	1	—	.....
.....	2.0	—	1	.....
.....	1.0	—	1	.....
.....	0.5	—	1	.....
.....	0.1	—	1	.....

10. Goodman and Robinson: Unpublished work.

Case		
Gastric—		
1	Hyperchlorhydria and dilatation	Positive-Negative
2-6	Neurosis (5 cases in all)	Negative
7	Carcinoma	Negative-Positive
8-9	Toxic gastritis (?) (2 cases)	Negative
10	Chr. gastritis (2 times)	Positive
11	Gastroptosis and enteroptosis	Positive
12	Undiagnosed	Positive
13	Undiagnosed	Negative
Intestinal—		
14-15	Chr. constipation (2 cases)	Negative
16	Chr. appendicitis, *Ascaris lumbricoides*, and trichocephaliasis	Positive
17	Neoplasm of jejunum	Negative
Kidney—		
18	Uremia	Positive
19	Amyloid nephritis	Positive-Negative
20	Renal calculus and erysipelas	Positive
21	Acute parenchymatous nephritis	Positive
22	Acute parenchymatous nephritis	Negative
23-25	Chr. parenchymatous nephritis (3 cases)	Negative
26	Chr. parenchymatous nephritis with chorea	Positive-Negative
27	Chr. parenchymatous nephritis	Positive-Negative
Metabolic—		
28-33	Diabetes (6 cases of varying severity)	Negative in all
34	Gall-stones	Positive
35	Arthritis, neisserian	Negative
36	Arthritis deformans	Positive
37	Chr. family jaundice	Positive-Negative
38	Chr. family jaundice	Strong
39	Chr. family jaundice	Negative
40	Hepatic cirrhosis	Strong
41	Multiple serositis	Negative
Blood—		
42-45	Progressive pernicious anemia (4 cases)	Negative
46	Progressive pernicious anemia	Very faint negative
47	Progressive pernicious anemia	Positive
48	Lymphatic leukemia	Positive
49	Myelogenous leukemia	Negative
50	Splenomegaly	Positive
Heart—		
51-52	Myocarditis (2 cases)	Negative
53	Chr. in. myocarditis	Negative
54	Chr. in. myocarditis	Negative
55	Mitral regurgitation	Negative
56-66	Normal cases (11 stools from 3 cases)	All Negative

NOTES OF CASES

CASE 1.—Hypertrophy and dilatation of stomach. This was positive to blood of that case while it did not hemolyze foreign blood-cells.

CASE 7.—Gastric carcinoma was at first negative, but a few days later proved to be positive.

CASE 19.—Amyloid nephritis. This was positive at first but later negative as were Cases 26 and 27, both chronic nephritis.

CASE 38.—Chronic family jaundice. This was at first strongly hemolytic and later negative while Case 40, hepatic cirrhosis, was strong but not complete.

CASE 47.—Progressive pernicious anemia. This was complete with same cells but only very slight with normal foreign cells.

To avoid any influence that might be brought about by the increased fragility of individual cases, red blood-cells from a normal case, that is, red blood-cells capable of resisting hemolysis in hypotonic salt solutions down to .44 per cent. NaCl, were used.

It will be observed from the above table that normal stools repeatedly, and stools from progressive pernicious anemia and gastro-intestinal diseases frequently, were negative, and that the results are not analogous to those of Külbs, whose procedure was quite similar to the above. Nor is there any analogy to the results of Bloch, who, in his series of ten cases, used an ethereal and not a salt solution extract.

The properties of the filtrates were as follows: Light to dark brown, of fecal odor and of variable reaction, the latter playing no part in the hemolytic action of the stool. Nor was there any association between the type of food or use of purgatives and hemolysis. No acholic stools were examined. The presence of indoxyl in the urine, and of the phenol and amido groups in the filtrates had no relation to hemolysis, nor did the action of heat (58 C. for one hour) play any part. On prolonged standing the action became weakened and finally lost after seven days.

Fatty acids and neutral fats were present alike in active and inactive stools, as were precipitations of phosphates occasionally.

The results were so inconstant in my series of cases that I feel that no dependence should rest on this test, either as an aid to clinical diagnosis or as a means of enlightenment etiologically.

In conclusion I wish to extend my thanks to Dr. Stengel for the suggestion of this work and the use of the patients in his wards in the University hospital as well as to Drs. E. H. Goodman and Herbert Fox for their kind assistance.

EXPERIMENTAL OBSERVATIONS ON THE COAGULATION OF OXALATED PLASMA, WITH A STUDY OF SOME CASES OF PURPURA*

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Stimulated by Whipple's[1] study of the blood-plasma of purpura, and also by the availability of a few patients with purpuric manifestations, we undertook the study, from the point of view of clinical adaptability, of the methods of determining the coagulation properties of the blood-plasma of purpura. We found it necessary, however, in connection with this work, to study in detail the general principles of coagulation, and we therefore present our results under the two general heads of (1) "Experimental" and (2) "Clinical Studies."

EXPERIMENTAL STUDIES

In the course of our early work we were impressed with the ease of preparing from dog's blood-cells a solution with great thromboplastic activity and comparatively so free from prothrombin or thrombin as to be available as a source of thromboplastin in clinical studies. This solution was prepared as follows: From a normal dog that had fasted twenty-four hours, blood from the jugular vein was allowed to flow into a 1 per cent. sodium oxalate solution in the proportion of nine parts of the former to one of the latter, which was immediately centrifugalized. The clear plasma was drawn off and preserved; the cells were washed three times with 0.85 per cent. sodium chlorid solution and then diluted with three volumes of distilled water. When hemolysis had occurred, 0.85 gram of sodium chlorid was added for each 100 c.c. of distilled water. This is quite similar to the solution of platelets prepared by Bayne-Jones; we have not, however, for our purposes found any advantage in isolating the platelets in pure form.

To determine whether this solution contained any considerable amount of thrombin or available prothrombin it was mixed with a solu-

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1. Whipple, G. H.: Hemorrhagic Disease. THE ARCHIVES INT. MED., 1912, ix, 365.

tion of pure fibrinogen prepared according to Howell's[2] method, except that dog's plasma was used instead of cat's plasma, as follows: 0.5 c.c. fibrinogen solution + 0.5 c.c. blood-cell solution + 0.3 c.c. $CaCl_2$ solution (2 per cent.). No clotting occurred in an hour, thus proving this solution to be free from thrombin or uncombined prothrombin.

To determine coagulation time the mixture to be tested was placed in a small test-tube and mixed by shaking. Once every half minute, from the time the calcium was added, a platinum loop was dipped into the mixture and the beginning of coagulation was arbitrarily fixed as the time when first a strand of fibrin could be drawn out of the fluid by the platinum loop. The platinum loop was then laid aside and once a minute the test-tube was tilted until it could be turned upside down without change of position of the clot; the time when this was possible was taken as the time of complete coagulation. This was the routine procedure in all experiments.

To determine whether the blood-cell solution contained any fibrinogen it was tested with a solution containing thrombin, obtained as follows: To 1 c.c. of dog's oxalated plasma was added 0.3 c.c. of calcium solution. When clotting was entirely completed the clot was removed and the fluid pressed from it. The resulting clear serum remained free from clot for an hour, but when added to fibrinogen solution clotting occurred. This serum was added with calcium to the blood-cell solution, as follows: 0.5 c.c. blood-cell solution + 0.5 c.c. serum + 0.3 c.c. calcium solution. No clotting occurred in an hour, proving the blood-cell solution to be free from fibrinogen.

That this solution shows the properties of Howell's thromboplastin is clearly demonstrated in the accompanying experiment (Table 1) with dog's oxalated plasma (D_2), which, on standing in the ice-chest for a few days, had lost some of its original activity.

TABLE 1.—EXPERIMENT DEMONSTRATING ACTION UPON DOG'S PLASMA

Plasma D_2 c.c.	Blood-Cell Solution, c.c.	Calcium Solution, c.c.	Begins, Minutes	Complete, Minutes
0.5	.....	0.15	7	15
0.375	0.125	0.15	1¾	3
0.25	0.25	0.15	⅓	2
0.125	0.375	0.15	1	1½
.....	0.5	0.15	*	..

*None in 1 hour.

Further experiments with this blood-cell solution follow:

On removing the clot that had formed after adding calcium to plasma D_2, a serum was left which would not cause the clotting of a

2. Howell, W. H.: The Preparation and Properties of Thrombin, Together with Observations on Antithrombin and Prothrombin. Am. Jour. Physiol., 1910, xxvi, 453.

solution of fibrinogen. On the subsequent addition, however, of the blood-cell solution clotting was prompt; for example:

0.5 c.c. fibrinogen solution + 0.5 c.c. serum D_2 + 0.3 c.c. calcium; no clotting in seventeen minutes.

On adding 0.5 c.c. blood-cell solution: Clotting begins, three minutes; complete, four and one-half minutes.

This experiment was repeated with a slight variation as follows:

0.5 c.c. fibrinogen solution + 0.5 c.c. blood-cell solution + 0.3 c.c. calcium; no clotting in eighteen minutes.

On adding 0.5 c.c. serum D_2 clotting begins, two minutes; complete, four minutes.

A slightly different result was obtained when the blood-cell solution and serum D_2 and calcium were allowed to stand together with the subsequent addition of fibrinogen solution; thus:

0.5 c.c. blood-cell solution + 0.5 c.c. serum D_2 + 0.3 c.c. calcium.

No clotting in fourteen minutes. On then adding 0.5 c.c. fibrinogen solution a small distinct clot formed after 18 minutes, but never clotted solidly.

It is evident that clotting occurred only when all four solutions were combined, the fibrinogen, the serum, the blood-cell solution and calcium; no three of these sufficed to produce coagulation.

The explanation which we offer for these experiments is based on Howell's theory. On standing in the cold the prothrombin of plasma D_2 was to a considerable extent bound by antithrombin, causing a delayed clotting time. On the addition of blood-cell solution, however, the prothrombin-antithrombin combination was broken up and prothrombin rendered available. In the serum left after clotting plasma D_2, all the prothrombin is apparently combined with antithrombin and is inactive until set free by the addition of the blood-cell solution.

With a view to determining the source of this thromboplastin in the blood-cell solution, the blood-cells of oxalated plasma were centrifuged. White blood-cells from the upper layer were collected and after repeated washing treated with three volumes of distilled water. Erythrocytes from the bottom of the centrifuge tube were collected separately, and after washing, were hemolyzed in three volumes of distilled water. The remaining cells of the middle layer were then mixed and similarly washed and hemolyzed. These three solutions so obtained were then tested in ascending dilutions for their power of accelerating the coagulation of a dog's oxalated plasma. This power was found to disappear in each of the three solutions at approximately the same dilution. The thromboplastin was not, therefore, derived exclusively from the leukocytes, nor erythrocytes, but can be obtained, as also shown by Howell[3] and by

3. Howell, W. H.: The Nature and Action of the Thromboplastic Substance of the Tissues. Am. Jour. Physiol., 1912, xxxi, 1.

Bayne-Jones,[4] from any of the blood-cells, but particularly from the blood-platelets.

For our purpose, the study of clinical cases, this solution of thromboplastin is to be preferred to the commonly-used tissue extracts, because of its greater ease of preparation and its greater activity.

To determine whether the destruction of prothrombin or its fixation by antithrombin could be hastened by exposure of the dog's oxalated plasma to heat, the plasma was kept at 47 C. for half an hour. This usually retarded coagulation (see Table 2), but the effect varied in different plasmas.

TABLE 2.—RETARDATION OF COAGULATION BY SUBJECTING DOG'S OXALATED PLASMA TO HEAT

Plasma D_3, c.c.	$CaCl_2$, c.c.	Clotting	
		Begins, Minutes	Complete, Minutes
1	0.3	3	5
1*	0.3	4	6
1†	0.3	9	18

*After heating to 47 C. for 15 minutes.
†After heating to 47 C. for 30 minutes.

If, however, such a heated plasma was allowed to stand at room-temperature for twenty-four hours, clotting either did not occur on the addition of calcium solution, or was very much delayed (see Table 3 [3]). The thromboplastin solution, however, still exerted a markedly accelerating effect on the coagulation of such heated plasma (see Table 3 [4]) and restored the coagulation time to a point close to that found before heating (see Table 3 [1 and 2]).

TABLE 3.—RETARDATION OF CLOTTING OF HEATED PLASMA AFTER STANDING FOR TWENTY-FOUR HOURS

	Plasma D_3, c.c.	$CaCl_2$, c.c.	Thromboplastin Solution, c.c.	Clotting	
				Begins, Minutes	Complete, Minutes
1	1	0.3	....	2	4½
2	0.75	0.3	0.25	1½	2
3	1*	0.3	....	†	...
4	0.75*	0.3	0.25	2½	3

*Plasma D_3 heated at 47 C. for one hour and kept at room temperature 24 hours. †No clot in 30 minutes.

The addition of one drop of thromboplastin to Tube 3 after it had stood for thirty minutes with no clotting, caused clotting to commence in two and one-half minutes; complete clotting occurred in five minutes. It would appear that the higher the temperature at which the oxalated plasma is allowed to stand, up to 58 C., the more rapid and the more

4. Bayne-Jones, S.: The Presence of Prothrombin and Thromboplastin in the Blood Platelets. Am. Jour. Physiol., 1912, xxx, 74.

complete is the disappearance or fixation of its available prothrombin. An abundance of prothrombin is, however, rendered available again on addition of a thromboplastin solution. In this connection it is of interest to note that Blaizot[5] has shown that an antithrombin develops in dog's oxalated plasma on standing in the cold.

INFLUENCE OF HEMOGLOBIN IN THE PLASMA ON THE ESTIMATION OF FIBRINOGEN

The observation that when the thromboplastin solution is heated to 58 to 60 C., a marked precipitation occurs, called attention to a possible occasional source of error in the estimation of fibrinogen by Whipple's method.[1] The following experiment in which a blood-cell solution and oxalated plasma have each been treated as in Whipple's method illustrates this:

Five c.c. of the thromboplastin solution were placed in a graduated centrifuge tube. A like quantity of a dog's clear oxalated plasma was placed in a similar tube. Both tubes were kept in a water-bath at 58 to 60 C. for fifteen minutes and then centrifuged for twenty-five minutes. In the tube containing the plasma was found a sediment of 0.2 c.c. of coagulated fibrinogen; in the tube containing the hemolyzed blood-cells, a sediment of 1.8 c.c. We have already seen that the blood-cell solution is quite free from fibrinogen (see above). It is evident, therefore, that proteins other than fibrinogen, which are coagulated at 58 to 60 C., are liberated from the blood cells on laking. The estimation of fibrinogen by heating to this temperature, therefore, becomes inaccurate if the plasma shows the least evidence of being tinged with hemoglobin.

CLINICAL STUDIES

In the clinical study of coagulation we believe that advantage can be taken of the thromboplastin solution described above for demonstrating the presence of prothrombin combined with antithrombin, and that this is an excellent method for detecting an increase in the antithrombin of the blood.

For the clinical study of coagulation we would, therefore, suggest the following steps in addition to a complete blood count and a careful enumeration of the blood-platelets:[6]

1. Estimation of the coagulation time of a drop of blood from the finger with one of the clinical coagulometers.
2. Take 20 c.c. of blood from a vein of the arm and mix with 2 c.c. of 1 per cent. sodium oxalate solution and centrifugalize.

5. Blaizot, L: Extractions de substances anticoagulants du plasma normal de chien. Compt. rend Soc. de Biol., 1911, lxx, 560.

6. Duke, W. W.: The Pathogenesis of Purpura Hemorrhagica with Especial Reference to the Part Played by the Blood-Platelets. THE ARCHIVES INT. MED., 1912, x, 445.

(a) To 1 c.c. of plasma so obtained add 0.3 c.c. of a 2 per cent. calcium chlorid solution and determine beginning and complete clotting. *If delayed,*

(b) To 0.75 c.c. of the original plasma add 0.25 c.c. of blood-cell solution prepared as described, and 0.3 c.c. of 2 per cent. calcium chlorid, and determine beginning and complete clotting. *If delayed,*

(c) To 0.5 c.c. of plasma add 0.5 c.c. pure fibrinogen solution and 0.3 c.c. of 2 per cent. calcium chlorid solution and determine beginning and complete clotting.

A delay in (1) but not in (2-a) suggests that there is not sufficient calcium available in the blood for normal coagulation, but that the other constituents are normal; a delay in (2-a) but not in (2-b) suggests that much of the prothrombin present is bound by antithrombin and is therefore inactive. A poor coagulation in (1), (2-a) and (2-b) but good in (2-c) suggests that there is a deficiency of fibrinogen which can be further confirmed at (3) (see below).

A delay in (1), (2-a), (2-b) and (2-c) suggests a deficiency of prothrombin, bound or unbound, with or without a deficiency of fibrinogen.

3. Precipitate fibrinogen in 10 c.c. of plasma by heating to 58 to 60 C. for 15 minutes on a water bath. Centrifugalize in a graduated tube for 25 minutes and read amount of sediment in volume per cent. This method is useless if plasma is discolored with hemoglobin (see above).

It may be noted here that a poor filmy clot may result quite as readily from a lack of thrombin as from a lack of fibrinogen in spite of statements in the literature to the contrary. We have repeatedly observed this type of clot in working with solutions of pure fibrinogen in abundance, but containing only a trace of thrombin.

This is shown by the following experiment:

Plasma D_2 was clotted in the usual manner and the serum was expressed from the clot. On the addition of fibrinogen to the serum another clot formed and serum was again expressed; this was repeated several times, the clot becoming poorer and smaller each time. An excess of calcium was constantly maintained. The addition of fibrinogen solution to the expressed serum finally resulted in merely a few threads of clot after thirty minutes, due to the exhaustion of the thrombin.

CLINICAL CASES

Of the twelve patients whom we have studied clinically, five showed purpura, one jaundice and one severe anemia; the other five were controls of various kinds. The five patients showing purpura were of various types. Our studies of three will be described in detail.

The first is a woman, aged 24, who throughout her life had been subject to subcutaneous hemorrhagic extravasations. These had not disturbed her until the previous five years, during which time the appearance of the extravasations had been preceded by pain, usually localized to that portion of the body where the purpuric manifestations later appeared. Her general health had not been affected. She gave the interesting history that three sisters, her mother and a maternal aunt have all presented similar purpuric lesions; only the aunt, however, suffered pain at the time of the attacks.

The examination of the patient's blood showed: Hemoglobin, 69 per cent.; red blood-cells, 4,580,000; leukocytes, 8,400. Differential count: Polymorphonuclears, 57 per cent.; small lymphocytes, 36 per cent.; large mononuclears, 2 per cent.; transitionals, 1 per cent.; eosinophils, 2 per cent.; basophils, 2 per cent. Blood platelets (preserved by formaldehyd solution) 215,300 per c.mm. Fragility of erythrocytes in hypotonic sodium chlorid solution:

	NaCl Solution—Per Cent.			
	0.3	0.35	0.4	0.45
Reading after 1 hour	+	±	±	—
Reading after 24 hours	+	+	±	—

Coagulation of blood: Bogg's coagulometer, eight minutes (average of three readings). Wassermann reaction, negative (examination by Dr. John Laird).

STUDY OF OXALATED PLASMA

Coagulation time was as follows: 1 c.c. plasma + calcium 0.3 c.c.; clotting began in sixteen minutes; complete in twenty-seven minutes. The influence of thromboplastin was shown as follows: 0.75 c.c. plasma + thromboplastin solution 0.25 c.c. + calcium 0.3 c.c.; clotting began in four minutes; complete in ten and one-half minutes. Equal parts of this plasma and of normal dog's plasma clotted as promptly as the dog's plasma alone. Fibrinogen content was 3 per cent. by volume.

At a later examination, after a month's interval, similar results were obtained. The red blood-cell count was 4,520,000; the platelets, 226,000. Coagulation of the blood: Bogg's coagulometer, 6 minutes.

STUDY OF OXALATED PLASMA ON SECOND TEST

Coagulation time was as follows: 1 c.c. plasma + calcium 0.3 c.c.; clotting of her oxalated plasma, which delay entirely disappeared on addition of thromboplastin was as follows: 0.5 c.c. plasma + 0.5 c.c. thromboplastin solution + calcium 0.3 c.c.; clotting began in four minutes; complete in nine minutes.

This patient showed, therefore, at two examinations a delay in coagulation of her oxalated plasma, which delay entirely disappeared upon addition of thrombo plastin. We are inclined to believe, therefore, that her plasma had an excess of antithrombin.

Another patient with simple purpura was a girl of 24 whose history was negative previous to two years before admission. At that time purpuric manifestations appeared and have continued to be present almost constantly since. Her symptoms consisted of hematemesis, epistaxis, bleeding from the gums, marked subcutaneous petechiae and furunculosis. A slight tendency to prolonged bleeding from cuts had been noticed. This did not begin, however, in childhood and no family history of hemophilia was obtained. Physical examination was negative except for the signs of severe anemia. Examination of the blood gave the results shown in Tables 4, 5 and 6.

TABLE 4.—BLOOD-ANALYSIS IN A CASE OF PURPURA HEMORRHAGICA

Date	Hgb., Per cent.	R. B. C.	W. B. C.	Poly. Per cent.	Lymph. Per cent.	Mono. Per cent.	Trans. Per cent.	Eosin. Per cent.	Myel. Per cent.	Baso. Per cent.
5/31/12	20	3,000,000	7,680	74	20	5	1	—	—	—
6/ 3/12	—	—	—	65	27	5	1	1	1	—
6/ 8/12	25	2,500,000	7,040	59	36	3	1	—	—	1
6/15/12	30	3,160,000	—	—	—	—	—	—	—	—
7/ 8/12	50	4,170,000	—	—	—	—	—	—	—	—
7/18/12	60	4,240,000	6,900	—	—	—	—	—	—	—
7/24/12	65	4,950,000	8,100	—	—	—	—	—	—	—
8/ 4/12	75	4,270,000	9,300	80	17	1	2	—	—	—
8/26/12	67	3,700,000	6,100	82	15	1	—	—	—	2

Platelets—6/25/12, 67,000; 7/29/12, 28,500; 8/30/12, 25,000.

TABLE 5.—FRAGILITY OF RED-CELLS

NaCl, Per Cent.	Reading* After 2 Hours	Reading After 24 Hours	Reading† After ½ Hour	Reading† After 24 Hours
0.2	100	100	100	100
0.3	100	100	100	100
0.325	+++	100	...	...
0.35	++	+++	++	++
0.375	++	++	tr.	tr.
0.4	++	++	tr.	tr.
0.425	+	+	..	..
0.45	+	+	0	0
0.475	tr.	tr.	..	..
0.5	ft. tr.	ft. tr.	0	0
0.525	0	ft. tr.	..	..
0.55	0	ft. tr.	0	0
0.6	0	ft. tr.	..	..

*6/18/12. †8/8/12.

Wassermann Reaction: Negative (Dr. Laird).

Blood-Culture: Mycobacterium Hoffmanni (Examination by Dr. Herbert Fox).

Coagulation of Blood: Using the Biffi-Brooks instrument, coagulation was found to commence in six minutes and to be completed in twelve minutes.

Coagulation of oxalated plasm, as determined by a number of readings, was between four and one-half and six minutes for the beginning and nine and one-half and twelve for the complete clotting. This is within normal limits.

This plasma, as tested on June 15, 1912, had no influence on the clotting of normal dog's plasma (see Table 6).

TABLE 6.—EFFECT OF PLASMA FROM PURPURIC PATIENT ON COAGULATION OF DOG'S PLASMA

Plasma B., c.c.	Plasma Dog, c.c.	$CaCl_2$, 2% c.c.	Begin, Minutes	Complete, Minutes
—	1	0.3	3	6½
0.05	0.95	0.3	3	5½
0.25	0.75	0.3	3	5½
0.5	0.5	0.3	3	6
0.75	0.25	0.3	4	9½
0.95	0.05	0.3	4⅔	11½
1	—	0.3	4¼	9½

The fibrinogen content of the slightly hemoglobin-stained plasma was found to be a little less than 10 per cent. by volume, but this high reading was doubtless due to contamination of the plasma with products of hemolysis.

Everything is normal in this case except the severe secondary anemia and the marked reduction of platelets. We have normal coagulation, which is the usual finding in purpura, and indeed it may truly be said that the factor determining purpura is not constantly involved in coagulation as studied in oxalated plasma.

Very similar findings were shown in a patient with hemophilia, a woman aged 30, who was admitted suffering from persistent, profuse metrorrhagia with a resulting anemia. A history of hemophilia in the patient and the patient's father was obtained. This transmission of hemophilia from father to daughter, with appearance of symptoms in the daughter, while not the usual history, has been observed. The blood showed:

Aug. 10, 1912: Hgb., 37 per cent.; R. B. C., 2,140,000; W. B. C., 11,700; Poly., 87 per cent.; Lymph., 11 per cent.; Mono., 2 per cent.; Trans, —; Eosin., —.

Aug. 16, 1912: Hgb., 38 per cent.; R. B. C., 2,430,000; W. B. C., 12,100; Poly., 79 per cent.; Lypmh., 14 per cent.; Mono., —; Trans., 6 per cent.; Eosin., 1 per cent.

Morphology, normal, no nucleated forms of erythrocytes. Platelets, 37,000.

Fragility: NaCl per cent.....	0.25	0.3	0.35	0.4	0.45	0.5
Reading after 20 min.	+	+	±	±	—	—
Reading after 24 hours	+	+	±	±	—	—

Coagulation of the blood measured with the Biffi-Brooks coagulometer gave beginning coagulation in eight, and complete coagulation in fifteen minutes.

Here again a normal coagulation time was seen in the presence of a reduced platelet count.

Among the cases observed was one of cholelithiasis with intense jaundice of over a month's duration. The blood-count was normal.

Hgb., 70 per cent.; R. B. C., 4,000,000; W. B. C., 5,300; differential: Poly., 64 per cent.; Lymph., 27 per cent.; Mono., 5 per cent.; Trans., 2 per cent.; Eosin., 1 per cent.; Baso., 1 per cent.

The clotting time of the blood of this case was moderately delayed as estimated with the Biffi-Brooks instrument, clotting commencing but little before ten minutes. On the other hand, the oxalated plasma, on the addition of an excess of calcium chlorid, clotted unusually rapidly in two and one-half minutes. Here the delayed coagulation time as measured in the whole blood was unquestionably due to the union of the calcium of the blood with bile pigments. Pure bile added to normal plasma *in vitro* does not delay the time of coagulation in the presence of an excess of freshly added calcium solution, but, on the contrary, slightly accelerates it as do many foreign solutions. The following protocol is illustrative:

Plasma D_3, c.c.	Bile Solution, c.c.	$CaCl_2$, 2% c.c.	Begin, Minutes	Complete, Minutes
1	—	0.6	3	4½
0.95	0.05	0.6	1½	2
0.75	0.25	0.6	2	3
0.5	0.5	0.6	2	15

In lower dilutions no clotting occurred. If, however, the solution of bile is allowed to act for ten minutes on the calcium solution before the resulting mixture is added to the plasma, there is very distinct delay of complete coagulation and such clot as is found is poor and filmy.

CONCLUSIONS

1. A solution of hemolyzed blood-cells is the most readily prepared and active thromboplastic solution.

2. A delay in coagulation time of oxalated plasmas occurs on heating or standing. This is due to the formation of antithrombin, and to the union of antithrombin with prothrombin. The coagulation time in such plasmas is greatly hastened by the addition of thromboplastin solution.

3. The presence of hemoglobin in a plasma is a source of error in the determination of fibrinogen by Whipple's method.

4. The scheme presented for the study of clinical cases is easily carried out and covers the essential points included in the present knowledge of this subject.

5. No method of study has as yet offered a satisfactory explanation of purpura.

PRIMARY CARCINOMA OF THE LARGER BRONCHI

AN ANALYSIS OF NINETY CASES WITH REGARD TO PATHOLOGY, SYMPTOMATOLOGY AND DIAGNOSIS; AND REPORT OF A NEW CASE*

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The large number of case reports of lung and bronchial neoplasms which have appeared in the literature in the last two years gives evidence of a renewed interest in this subject. Two factors have served to draw attention to its importance. There has been a growing realization of the fact that bronchial and pulmonary carcinomata are by no means as rare as was once thought, and the developing possibilities of intrathoracic surgery have made their early diagnosis a matter of more than scientific curiosity. It is hoped that the analysis of a large number of carefully selected cases of primary carcinoma of the larger bronchi will aid in forming a definite clinical picture for this condition and in taking it out of the mixed group of lung and bronchial neoplasms in which it has usually been considered. Even Adler,[1] who has written the most extensive of the recent monographs on the subject, does not attempt to separate the two types in his list of cases.

Several attempts have been made to collect from the literature the cases of primary carcinoma of the lungs and bronchi. Reinhard[2] found 25 cases in 1878, Wolf[3] 31 cases in 1895, and Adler[1] 374 cases in 1911. These authors, however, admitted to their lists cases without microscopical verification of their carcinomatous nature. In 1891, Werner[4] could find but nine cases fully verified, while in 1896 Pässler[5] listed about 70 such. In differentiating between carcinoma and sarcoma, in ruling out tuberculous processes, and especially in examining metastases and considering the possibility of a primary growth elsewhere, microscopical examinations become necessary, and a statistical study loses in value in proportion as it includes unverified cases.

Wolf[2] separated the cases which he listed into those primary in the lung parenchyma and those having their origin from the larger bronchi.

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*From the Pathological Laboratory of the University of Michigan, Ann Arbor, Michigan.

1. Adler, J.: Primary Malignant Growths of the Lungs and Bronchi, 1911.
2. Reinhard, W.: Arch. d. Heilk., 1878, xix, 369.
3. Wolf, K.: Fortschr. d. Med., Berlin, 1895, xiii, 725.
4. Werner, M.: Das primäre Lungencarcinom. Dissert., Freiburg, 1891.
5. Pässler, H.: Arch. f. path. Anat., Berlin, 1896, cxlv, 191.

He placed twenty-three of his thirty-one cases in the second group. It is often found impossible to determine even roughly the point of origin of the growth, because of the enormous size of the neoplasm and the widespread involvement of surrounding structures, but there is a large group in which the bronchial origin may be established. Obviously the symptomatology of these cases differs very much from that of cases in which the neoplasm is located in the peripheral portions of the bronchial tree. This difference has been referred to by Pässler,[8] but he does not group the cases accordingly in compiling his clinical statistics.

Fig. 1.—Right lung showing right main bronchus (Br.) cut across. Its lumen is much reduced by the surrounding carcinomatous infiltration.

It is the purpose of this study to collect the authenticated cases of primary carcinoma of the larger bronchi and investigate the pathological and clinical features of this group. Only those cases meeting the following requirements have been admitted:

1. An autopsy must have been performed.
2. The carcinomatous nature must have been verified microscopically.
3. There must be no reasonable suspicion that the neoplasm is not a primary growth.

4. There must be good evidence of bronchial origin. This may be found either in the gross relationship of the tumor to a bronchus or in the microscopical relationship of the neoplasm to bronchial elements.

As far as possible the following list has been made to include all cases meeting the above tests. The original reports have been used wherever access could be had to them, but full acknowledgment is made of data from Adler's recent monograph[1] in regard to twenty cases in which the original sources were not obtainable. It has also been possible to include nineteen cases which are not found in his somewhat earlier compilation. Beyond a doubt there are many other cases of bronchial carcinoma in the literature, but they cannot find a place here because they fail to meet one or more of the criteria previously mentioned.

SYNOPSIS OF REPORTED CASES

1. ALLAN.[6] 1907, M., 38. Pain in left chest and arm; dyspnea; palpable tumor at origin of left sternomastoid; left pupil contracted, ptosis of left lid, left vocal cord fixed in cadaveric position. Left main bronchus blocked by encircling tumor mass of scirrhous type, with large masses of cells; metastases in bronchial nodes and left lobe of thyroid.

2. BECK.[7] 1884, M., 65. Blacksmith. Alveolar carcinoma of right main bronchus and its branches. Lumina constricted; cavity in right upper lobe; secondaries in right bronchial nodes, mediastinal pleura, thyroid, liver, both adrenals; superior vena cava involved and thrombosed; origin from mucous glands.

3. BECK.[7] 1884., F., 57, charwoman. Primary alveolar carcinoma of right main bronchus and its chief branches; polyhedral cells; bronchial nodes at hilus secondarily involved; stenosis of superior vena cava; origin from bronchial mucous glands.

4. BOECKER.[8] 1910, F., 83, housewife. Tumor mass reaching from hilus to pleura in right lower lobe; situated about two medium sized bronchi; alveolar in structure with mucus formation; secondaries in tracheal and cervical nodes (?) not microscopically examined.

5. BOYD.[9] 1887. M., 38. Bottle-blower. Cough, dyspnea, cyanosis, blood-tinged sputum, veins of forehead and neck dilated; edema of right arm and face; voice hoarse and aphonic; carcinoma extending to the right from region of bifurcation and compressing vena cava.

6. DELORME [10] (After Adler). 1901, M., 25. Cough, fever, blood tinged sputum; dilated veins; paralytic symptoms; secondary nodules; cylindric celled carcinoma of left chief bronchus; secondaries in pericardium, pleura, skull, suprarenals, liver, various long bones, sternum, ribs and lymph-nodes.

7. DAVIS AND LE COUNT.[11] 1908. M., 58. Saloonkeeper. Cough, blood-streaked sputum; glandular masses in neck and axilla; dulness and increased fremitus over upper left; hoarseness, dyspnea, cyanosis; paralysis of left vocal cord; carcinoma of left main bronchus, in part adenomatous with mucin-like content; origin from mucous glands.

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6. Allan, G. A.: Lancet, London, 1907, ii, 961.

7. Beck: Ztschr. f. Heilk., 1884, v.

8. Boecker, E.: Zur Kenntniss der primären Lungenkarzinome. Inaug. Dissert., Berlin, 1910.

9. Boyd: Lancet, London, 1887, ii, 60.

10. Delorme: Ueber primäres Lungencarcinom. Dissert., Jena, 1901.

11. Davis and Le Count: Chicago Path. Soc., 1908, vii, No. 5.

8. Davis and Le Count.[11] 1908. F., 32. Dyspnea, cough, blood-stained sputum, hoarseness; left chest fixed and bulging; mucosa of chief bronchi resembled skin; left main bronchus almost occluded by squamous-celled carcinoma; left lung airless; metastases in tracheal and retro-aortic nodes, pleura, liver, both adrenals, both kidneys and both ovaries.

9. Dömeny.[12] 1902. M. Sharp pain in left side; cough with scanty sputum; medullary carcinoma of bronchus to left lower lobe; atelectasis of that lobe; emphysema of right lung; secondaries in lymph-nodes and right kidney; origin from bronchial epithelium.

10. Dömeny.[12] 1902. F., 79. Right hydrothorax; carcinoma of left main bronchus; branch to lower lobe nearly obstructed; large nests of polygonal cells; secondaries in bronchial nodes.

11. Dömeny.[12] 1902. M., 41. Pain in head, auditory and visual disturbances; choked disk on both sides; cylindric celled adenocarcinoma of bronchus to left lower lobe; that lobe atelectatic; seven brain metastases; origin from mucous glands.

12. Dömeny.[12] 1902. F., 66. Fever, cough, pain in right side, dyspnea; dulness below angle of scapula on the right; cylindric celled adenocarcinoma of bronchus to upper right lobe; secondaries in bronchial and mediastinal nodes; origin from mucous glands.

13. Dömeny.[12] 1902. M., 29. Pain in left arm; tumor masses on ribs, sternum and cranium; adenocarcinoma of bronchus to left lower lobe; secondaries of cranium, ribs, sternum, liver, retrobronchial and retroperitoneal nodes, brain, right kidney; much mucus formation, especially in metastases; origin from mucous glands.

14. Dorsch.[13] 1886 (After Pässler). F., 54. Two medullary masses in right upper lobe, growing from right chief bronchus and involving pericardium and vena cava; the latter thrombosed; large polymorphous cells; metastases in lymph-nodes at hilus, lung tissue of same side, liver, spleen, kidneys, sternum, dura mater.

15. Ehrich.[14] (After Adler). 1891. M., 51. Dulness over upper right; hemoptysis; cancerous tissue in sputum; large node in right axilla; alveolar carcinoma of right main bronchus; polymorphous cells; secondaries in pericardium, chest wall, bronchial nodes and diaphragm; origin from mucous glands.

16. Ehrich[14] (After Adler). 1891. F., 56. Clinical diagnosis, tumor of mediastinum; alveolar carcinoma of lower trachea, right chief bronchus and its branches; polymorphous cells; right lung atelectatic; metastases in bronchial and mediastinal lymph-nodes, left lung, liver, heart.

17. Ernst.[15] 1896. M., 50. Cerebral symptoms, cough and mucopurulent sputum; bronchus to right upper lobe occluded by papilliferous growth; squamous-celled carcinoma; metastases in left adrenal, cerebrum and cerebellum.

18. Fränkel.[16] 1904. M., 52. Laborer. Pain in left chest; cough; blood-stained sputum; enlarged inguinal gland found to be carcinomatous; occlusion of left main bronchus by cylindric celled carcinoma; secondaries in inguinal and tracheal nodes.

19. Fränkel.[16] M., 40. Chill, high fever, dyspnea; mucopurulent sputum, later dirty brown; bronchus to right lower lobe nearly occluded by a cylindric-celled carcinoma; bronchiectasis; secondary involvement of nodes at hilus.

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12. Dömeny: Ztschr. f. Heilk., Wien, 1902, xxiii, 407.

13. Dorsch: Ein Fall von primären Lungenkrebs, Inaug. Dissert., Tübingen, 1886.

14. Ehrich: Ueber das primäre Bronchial- und Lungencarcinom. Dissert., Marburg, 1891.

15. Ernst, P.: Beitr. z. path. Anat., etc., Jena, 1896, xx, 155.

16. Fränkel, A.: Spezielle Pathologie u. Therapie der Lungenkrankheiten, 1904.

20. FRIEDLANDER[17] (after Pässler). 1885. M. White medullary mass proceeding from left upper lobe bronchus; no metastases; squamous-celled carcinoma with epithelial pearls.

21. GARBAT.[18] 1909. M., 64. Insurance agent. Asthenia, emaciation, cough, blood-stained sputum, night sweats; tumor mass over right scapula found to be carcinoma; central portion of right lung involved in mass of carcinomatous growth with mucus-containing alveoli; origin from mucous glands; secondaries in liver, both lungs, bronchial, supraclavicular and retroperitoneal nodes; old tuberculosis of left apex.

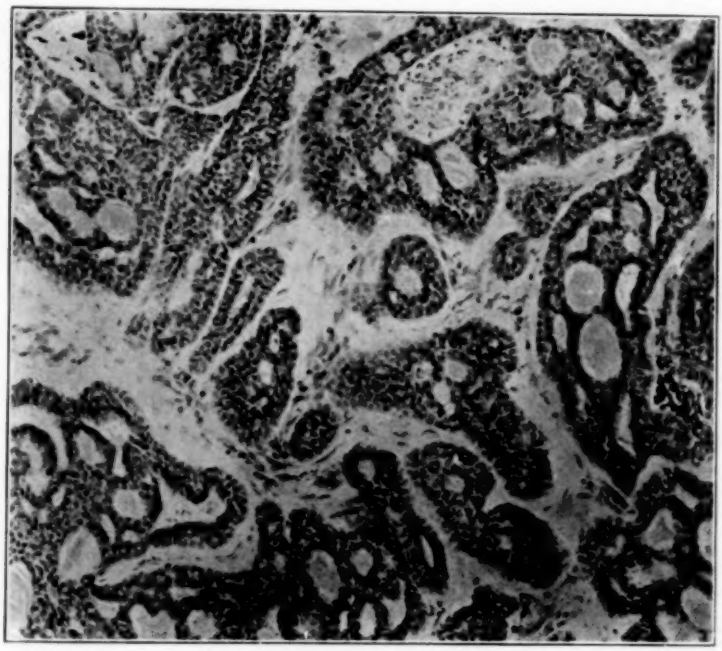

Fig. 2.—Section from the bronchial adenocarcinoma shown in Fig. 1. The alveolar spaces are filled with mucin. Zeiss obj. "B."

22. GEORGI.[19] 1879. M., 60. Blacksmith. History of trauma; cough developed with scanty sputum becoming bloody; died one year later; medullary carcinoma at hilus of left lung; bronchiectasis; upper left lung atelectatic; right emphysematous; no metastases.

23. GEIPEL.[20] 1899. M., 70. Cigar-maker. Symptoms of some severe pulmonary disease; upper main branch of left chief bronchus almost occluded by an alveolar cylindric celled carcinoma; secondaries in left lower lobe; origin from bronchial mucosa.

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17. Friedlander: Fortschr. d. med., 1885, i, 307.

18. Garbat, A. L.: Am. Jour. Med. Sc., 1909, N. S., cxxxvii, 857.

19. Georgi: Berl. klin. Wchnschr., 1879, xxviii and xxix.

20. Geipel: Centralbl. f. Allg. Path. u. path. Anat., 1899, x, 848.

24. GOUGEROT.[21] 1905. M., 46. Old tuberculosis; dyspnea, cough, mucopurulent sputum with Koch bacilli; dulness in upper right; polyuria; right main bronchus obstructed by growth which extended throughout upper portion of lung; squamous celled carcinoma with pearls; metastases in peribronchial nodes and left kidney.

25. HALL AND TRIBE.[22] 1905. M., 17. Cough, dyspnea, cachexia; blood-tinged sputum; glycosuria; columnar-celled carcinoma of bronchus to left lower lobe; secondaries in upper left lobe, liver, retroperitoneal and cervical nodes and calvarium.

26. HAMPELN.[23] 1897. M., 57. Chronic bronchial catarrh, emphysema, asthenia; bloody expectoration; dyspnea; primary bronchial carcinoma with polymorphous cells, origin from mucous glands; no metastases.

27. HANDFORD.[24] 1888. M., 64. Collier. Cough, dyspnea, rapid wasting; history of trauma received five months previously; blood-stained sputum; dulness over upper left thorax; growth beginning three-quarters of an inch above tracheal bifurcation and extending along left chief bronchus, nearly filling lumen; secondaries in left lung, pleura and liver; origin from bronchial mucosa; right lung emphysematous.

28. HANDFORD.[25] 1889. M., 63. Pain after taking food, cough, vomiting, weakness; no dulness; medullary carcinoma completely occluding lower primary division of left bronchus; left lower lobe collapsed; secondaries in liver and bronchial nodes; stomach symptoms due to ulcer.

29. HENRICI.[26] 1912. M., 62. Cough, bloody sputum; flatness on right between clavicle and fourth rib; squamous celled carcinoma of bronchus to right upper lobe; origin from bronchial mucosa.

30. HINTERSTOISSEN.[27] 1889. M., 59. Lieutenant-colonel. History of trauma; glandular swelling of left side of neck and right axilla; pain in left arm; tumor of right ring finger was found to be carcinoma; paralysis of left vocal cord; sputum often bloody and diagnosis made from cells in sputum; carcinoma simplex involving bifurcation and both main bronchi; secondaries in right axillary, left supraclavicular, bronchial and mediastinal nodes and terminal phalanx of right ring finger.

31. HITZ[28] (after Adler). 1887. F., 40. Fever, cough, dyspnea, dysphagia, bloody sputum; alveolar carcinoma of right main bronchus; bronchiectasis of right lung, emphysema of left; secondaries in regionary lymph-nodes.

32. HORN.[29] 1907. F., 18. Cough, dyspnea, pain in left thorax, hemoptysis; sudden death; left lung atelectatic; bronchiectasis; left main bronchus completely occluded by carcinoma of glandular structure; spaces contained colloid-like material; origin from bronchial mucosa.

33. JAPHA[30] (after Adler). 1892. M., 48. Dyspnea, pain, cyanosis, pleural effusion; dilated veins over thorax; bloody sputum with cancerous particles; cylindric and squamous celled carcinoma developing from hilus along right bronchial tree; metastases in lymph-nodes, pleura and pericardium; origin from bronchial mucosa.

34. KARRENSTEIN[31] (after Adler). 1908. M., 48. Hemoptysis; pain in right chest; dulness over right lung; bronchoscope showed tumor in right bronchus;

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21. Gougerot, H.: Bull. et mém. Soc. anat. de Par., 1905, lxxx, 294.
22. Hall and Tribe: Lancet, London, 1905, i.
23. Hampeln, P.: Ztschr. f. klin. Med., Berlin, 1897, xxxii, 247.
24. Handford, H.: Tr. London Path. Soc., 1888-9, xl, 40.
25. Handford, H.: Tr. London Path. Soc., 1889-90, xli, 37.
26. Henrici: Jour. Med. Research, 1912, xxvi, 395.
27. Hinterstoissen, H.: Wien. klin. Wchnschr., 1889, ii, 374.
28. Hitz: Ein Beitr. z. Casuistik des primären Lungencarcinoms. Dissert., Zurich, 1887.
29. Horn, O.: Virchows Arch. f. path. Anat., 1907, clxxxix, 414.
30. Japha: Ulcer primären Lungenkrebs. Dissert., Berlin, 1892.
31. Karrenstein: Charité Ann., 1908, xxxii, 315.

squamous celled carcinoma with pearls; metastases in liver, stomach, kidneys, brain (?) and pericardium; origin from bronchial mucosa.

35. KIDD.[32] 1892. M., 52. Butcher. Cough for twelve months; pain in left side, blood-streaked sputum, dyspnea, dulness and feeble breath sounds on left; tumor at bifurcation and along left chief bronchus and branch to upper lobe; bronchiectasis; atelectasis on left; secondaries in adrenal and jejunum (?).

36. KLÜBER[33] (after Adler). 1898. F., 34. Apparently healthy, sudden death following burn; glandular carcinoma with small cuboidal cells completely obstructing right lower main bronchus; bronchiectasis in right lower lobe; no metastases; origin from mucous glands.

37. KOERNER.[34] 1888. M., 64. Money loaner. Cough, bloody sputum; flatness and absent fremitus on right; severe dyspnea; right lung emphysematous; carcinoma occluding right chief bronchus.

38. KRETSCHMER[35] (after Adler). 1904. M., 54. Clinical diagnosis: purulent bronchitis, bronchiectasis, pleurisy, diabetes; alveolar carcinoma of left lower bronchus; no metastases; origin from mucous glands.

39. KRETSCHMER[35] (after Adler). 1904. M., 68. Left-sided pleural effusion; adenomatous carcinoma of left main bronchus; metastases in bronchial, mediastinal, retroperitoneal nodes, left kidney, liver, both adrenals. Origin from mucous glands.

40. KUBR.[36] 1906. M., 36. Pain in chest, cough, dyspnea, loss of weight and strength. Cylindric celled carcinoma arising from mucosa of trachea and bronchi, proliferating along bronchial ramifications and obstructing lumina; diagnosed from metastases.

41. LANGHANS.[37] 1871. M., 40. Symptoms of right bronchial stenosis; died suddenly in a "suffocative attack"; alveolar carcinoma at tracheal bifurcation and along wall of right bronchus; small polyhedral cells; no secondaries; origin from mucous glands.

42. LARDILLON[38] (after Adler). 1903. M., 60. Cough, emaciation, asthenia, mucopurulent sputum; alveolar carcinoma of left main bronchus; polymorphous cells; bronchiectasis and atelectasis of left lung; secondaries in nodes at left hilus.

43. LETULLE AND BIENVENUE[39] (after Adler). 1908. F., 63. Emaciation, hoarseness, dyspnea, blood-stained sputum; alveolar carcinoma of left main bronchus; polymorphous cells; secondaries in tracheal and bronchial nodes and adrenals; origin from bronchial mucosa.

44. MAUN[40] (after Adler). 1905. M., 50. Asthenia; abundant hemoptysis; alveolar carcinoma of left main bronchus; secondaries in bronchial nodes, pericardium, left ventricle; origin from bronchial mucosa.

45. MCINTYRE.[41] 1912. N., 67. Dyspnea, cough, bloody sputum; dulness over upper left; adenocarcinoma of bronchus to upper left lobe; no metastases; tuberculosis also present.

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32. Kidd, P.: Tr. Clin. Soc. London, 1892, xxv, 178.

33. Klüber: Ein Fall von Bronchialcarcinom und Lungencyste. Dissert., Erlangen, 1898.

34. Koerner, O.: München. med. Wchnschr., 1888, xxxv, 178.

35. Kretschmer: Ueber das primäre Bronchial- und Lungenkarzinom. Dissert., Leipzig, 1904.

36. Kubr: Centralbl. f. inn. Med., 1906, No. 44, p. 1089.

37. Langhans: Virchows Arch. f. path. Anat., xliii, 470.

38. Lardillon: Contribution à l'étude du cancer des poumons. Thèse de Lyon, 1903.

39. Letulle et Bienvenue: Bull. et mém. Soc. méd. d. hôp. de Paris, 1908, xxv, Series 3, p. 610.

40. Maun, J.: Deutsch med. Ztschr., 1905, xxvi, 537.

41. McIntyre: Glasgow Med. Jour., 1912, lxxviii, 95.

46. MERKLEN AND GIRARD[42] (after Adler). 1901. M., 45. Dyspnea, dysphagia, aphonia; dulness over right lung; blood-streaked sputum; alveolar carcinoma of right main bronchus; no metastases.

47. MEUNIER.[43] 1895. M., 70. Cabinet maker. Extreme dyspnea for eight days; semi-stuporous; cough; sputum blood-tinged; healed tubercles in left apex; tumor mass at hilus of right lung; alveolar structure, polyhedral cells; origin from bronchial glands.

48. MINSSEN[44] (after Adler). 1900. M., 43. Pain in right chest, cough, dyspnea, bloody sputum; alveolar carcinoma of right lower lobe bronchus; some mucus formation in neoplasm; secondaries in left pleura, bronchial and retroperitoneal nodes; pancreas, spleen, kidneys; origin from mucous glands.

49. OGLE.[45] 1893. F., 48. Left bronchus completely obstructed by polypoid growth near bifurcation; purulent material in bronchi; alveolar carcinoma; metastases in bronchial nodes.

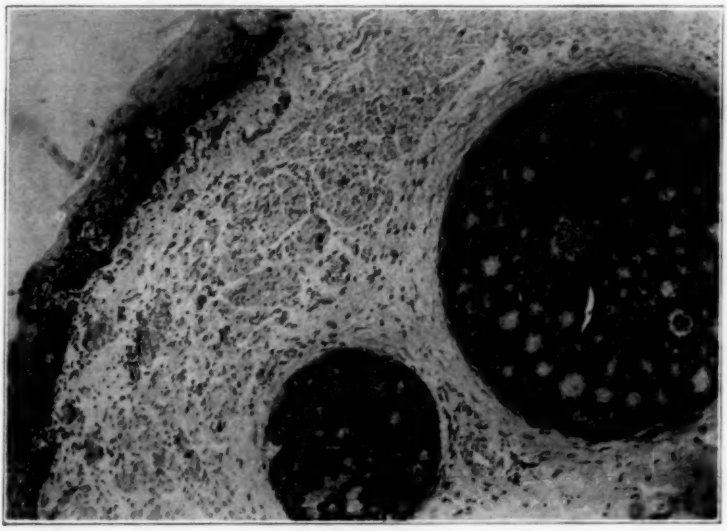

Fig. 3.—Wall of esophagus showing ingrowth of bronchial adenocarcinoma by direct extension. Zeiss obj. "B."

50. PACKARD.[46] 1905. M., 55. Cigarmaker. Cough, dyspnea, bloody sputum; dilated veins over thorax and flatness over entire right, with absent fremitus; enlarged abdomen; lymph-nodes in both axillae. Death from hemorrhage. Squamous celled carcinoma involving all of right main bronchus and part of left; secondaries in left lung and pleural surface of diaphragm.

51. PÄSSLER.[5] 1896. M., 73. Pensioned policeman. Cough and sputum, never bloody; left recurrent laryngeal paralysis; medullary cylindric celled carcinoma

42. Merklen and Girard: Bull. et mém. Soc. méd. d. hôp. de Paris, 1901, xviii, Series 3, p. 760.

43. Meunier, H.: Arch. gén. de méd., Par., 1895, i, 343.

44. Minssen: Ueber primären Lungenkrebs. Dissert., Kiel, 1900.

45. Ogle, C.: Tr. London Path. Soc., 1893-4, xlv, 25.

46. Packard, M.: Med. News, New York, 1905, lxxxvi, 303.

of left chief bronchus, compressing trachea; bronchiectasis in left lung, emphysema in right; secondaries in both kidneys.

52. PÄSSLER.[5] 1896. M., 52. Chronic laryngitis; repeated hemorrhages; small ulcerating squamous-celled carcinoma of right main bronchus; fatal hemorrhage from erosion of right pulmonary artery.

53. PÄSSLER.[5] 1896. M., 63. Nearly complete right sided hemiplegia; cachexia. Carcinoma of bronchus in left lower lobe; metastases in right lower lobe, liver, cerebrum and cerebellum; cylindric cell type with some mucous degeneration.

54. PAROW[47] (after Adler). 1896. M., 62. Dyspnea, cachexia, dysphagia. Tumor in right supraclavicular region; cylindric and polymorphous celled carcinoma of right main bronchus and first portion of left; metastases in cervical and supraclavicular nodes. Origin from bronchial mucosa.

55. PEABODY.[48] 1891. M., 33. Stevedore. Cough, mucoid expectoration, pain in left chest; impaired resonance over left, hyperresonance over right side; tumor mass 2¾ inches in diameter in and around left chief bronchus; metastases in lungs.

56. PERITZ[49] (after Adler). 1896. M., 48. Pain in right chest, cough, dyspnea, cachexia; flatness over entire right; bloody sputum; enlarged axillary and cervical nodes; alveolar cylindric celled carcinoma of right main bronchus; secondaries in mediastinal, mesenteric, axillary and cervical nodes, and liver. Origin from ducts of mucous glands.

57. PITT.[50] 1887. F., 67. Dyspnea; lessened motility of right chest; right main bronchus almost occluded by surrounding growth; bronchiectasis of right lung. Carcinoma of a glandular scirrhous type; metastases in left lung and right supraclavicular nodes.

58. REINHARD.[1] 1878. M., 47. Varnisher. Hoarseness, dyspnea, cyanosis, swelling of face and neck; pain in chest. Alveolar carcinoma of bronchus to right upper lobe, compressing superior vena cava; left lung emphysematous. Origin from mucous glands (?).

59. ROSENTHAL[51] (after Adler). 1899. F., 52. Hemiplegia and other cerebral symptoms; some cough and dyspnea. Alveolar cylindric celled carcinoma of left main bronchus; secondaries in brain, bronchial and tracheal nodes and left ventricle.

60. SCHRÖTTER[52] (after Nager). 1907. F., 57. Paralysis of left recurrent laryngeal. Squamous celled carcinoma at bifurcation of trachea completely blocking left chief bronchus.

61. SEHRT[53] (after Adler). 1904. M., 66. Alveolar squamous celled carcinoma of right main bronchus. Secondaries in bronchial and tracheal nodes; bronchiectasis; chronic tuberculosis; fatal hemorrhage following erosion of pulmonary artery.

62. SEHRT[53] (after Adler). 1904. M., 68. Dyspnea, dulness over left chest, hemoptysis. Squamous celled carcinoma of left main bronchus; secondaries in bronchial lymph-nodes and esophagus; chronic tuberculosis.

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47. Parow: Ein Fall von primären Lungencarcinom. Dissert., Greifswald, 1896.

48. Peabody, G. L.: Med. Rec., New York, 1891, xxxix, 438.

49. Peritz: Ueber Brusthöhlen Geschwülste. Dissert., Berlin, 1896.

50. Pitt, G. N.: Tr. London Path. Soc., 1887-8, xxxix, 54.

51. Rosenthal: Ueber einen Fall von primären Lungencarcinom. Dissert. München, 1899.

52. Schrötter: Klinik der Bronchoskopie, 1907. Quoted by F. R. Nager in Arch. f. Laryngol. u. Rhinol., Berlin, 1907, xx, 275.

53. Sehrt: Beiträge zur Kenntniss des primären Lungencarcinoms. Dissert. Leipzig, 1904.

63. Stieb[54] (after Adler). 1900. M., 50. Patient died of cirrhosis of liver. Submucous squamous-celled carcinoma of bronchus to left lower lobe; secondaries in regionary lymph-nodes.

64. Stieb[54] (after Adler). 1900. M., 60. Cough, pain, weakness. Alveolar squamous-celled carcinoma at bifurcation of right main bronchus; secondaries in both lungs and supraclavicular nodes.

65. Stilling.[55] 1881. M., 52. Alveolar carcinoma of bronchus to right middle lobe; large polygonal cells; metastases in bronchial, mediastinal and cervical nodes, pericardium and liver.

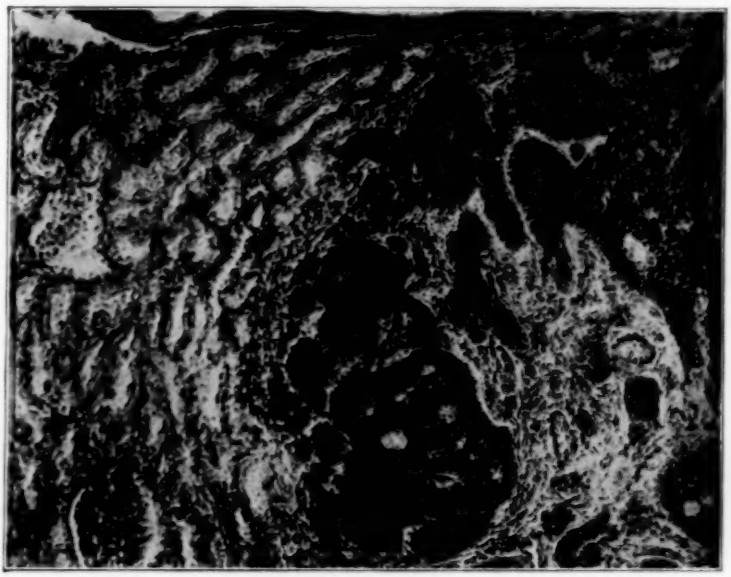

Fig. 4.—Metastatic growth in kidney from primary bronchial adenocarcinoma. The mucus formation is still present but not as marked as in the primary growth. Zeiss obj. "B."

66. Stropeni.[56] 1910. F., 35. Housekeeper. Pain in side, back and shoulder; cough; sputum blood-streaked. Subcutaneous carcinomatous nodule of left arm; fracture of left femur; left lung atelectatic; right lung emphysematous. Adenocarcinoma from mucous glands of left chief bronchus; secondaries in both lungs, epicardium, liver, both kidneys, spleen, right femur, thoracic and lumbar vertebrae and cranial vault.

67. Turnbull and Worthington[57] (after Adler). 1908. M., 56. Symptoms mainly referable to cord lesion. Mucus secreting carcinoma of bronchus to right lower lobe; secondaries in seventh and eighth dorsal vertebrae and in ribs.

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54. Stieb: Ueber das Plattenepithelcarcinom der Bronchien. Dissert. Giessen, 1900.

55. Stilling: Virchows Arch. f. path. Anat., 1881, lxxxiii, 77.

56. Stropeni, L.: Ztschr. f. Krebsforsch., Berlin, 1910, ix, 1-21.

57. Turnbull and Worthington: Arch. Path. Inst. London Hosp., 1908, ii, 163.

68. SCHRÖTTER.[58] 1907. M., 44. Cough and stabbing pain in right side; dilated veins on left chest, abdomen and arm; bloody sputum. Specimen from right main bronchus was found to be squamous-celled carcinoma with glycogen-containing cells; tuberculosis in right apex; emphysema of left lung.

69. WAGNER.[59] 1903. Cylindric celled carcinoma of left chief bronchus. Lumen of bronchus obstructed by cauliflower growth; metastases in left lung, anterior mediastinum, left lobe of liver. Origin from bronchial mucosa.

70. WATSUJI.[60] M., 56. Mucosa reddened and broken at origin of left chief bronchus. Near hilus a large tumor mass completely infiltrating bronchial wall; right lung emphysematous; squamous-celled carcinoma. Origin from bronchial mucosa.

71. WATSUJI.[60] 1904. M., 60. No clinical history. Squamous-celled carcinoma of left chief bronchus; metastasis in a bronchial node which also contained a caseating tubercle.

72. WATSUJI.[60] 1904. M., 59. Squamous-celled carcinoma of right lower lobe bronchus; right lung atelectatic; patient was also tuberculous.

73. WATSUJI.[60] 1904. Microscopical report without history or protocol; sections showed change of epithelium of a lower lobe bronchus into squamous type; wide peripheral extension from this bronchus.

74. WATSUJI.[60] 1904. M., 64. Tumor mass at point of division of bronchus to middle lobe; squamous-cell type with hyaline pearls.

75. WEINBERGER.[61] 1901. M., 42. Beadle. History of bronchitis and influenza; fever, cough, bloody sputum, stridor; dulness over upper right. Cylindric-celled carcinoma of secondary bronchus in right upper lobe; metastases in right infra- and supraclavicular and axillary nodes.

76. WEINBERGER.[61] 1901. M., 52. Clerk. Pain in right chest, cough, dyspnea. Blood-tinged sputum with carcinomatous tissue; walnut-sized tumor of parietal bone; right main bronchus completely obstructed by carcinoma; metastases in liver, kidney, muscles, intestines, parietal bone and brain.

77. WERNER.[62] 1891. M., 65. Farm laborer. Bloody sputum for ten weeks; pain in right axilla, hip, left forearm; atypical epithelial cells in sputum; three lower spinous processes painful; tumor of bronchus to upper left lobe; glandular structure; metastases in left arm (fracture), lower vertebrae, neck of right femur.

78. WEST.[63] 1884. M., 39. Laborer. Dyspnea, emaciation, asthenia, night sweats; dulness over lower right. Carcinoma surrounding right main bronchus, reducing its lumen to one-third; secondaries in bronchial nodes and liver.

79. WOLF.[3] 1895. M., 60. Symptoms of cavitation. Cylindric celled carcinoma encircling and stenosing left chief bronchus 2 cm. below the bifurcation; bronchiectasis; metastases in liver and bronchial nodes.

80. WOLF.[3] 1895. M., 54. Musician. Anorexia, asthenia, emaciation; in left chief bronchus an ulcerating tumor obliterating its branches; left lung small and firm, right lung emphysematous. Cylindric-celled carcinoma; metastases in bronchial glands and peritoneum.

81. WOLF.[3] 1895. M., 47. Blacksmith. Pain in right side, dry cough, dyspnea; dulness and bronchial breathing on right; right chief bronchus entirely closed by tumor reaching 1.5 cm. above the tracheal bifurcation; bronchiectasis on right; left lung emphysematous. Carcinoma simplex; large polymorphous cells; secondaries in lungs, dura mater and liver.

82. WOLF.[3] 1895. M., 42. Factory-hand. Clinical picture was that of brain tumor; right chief bronchus partially closed and its mucosa ulcerated; tumor

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58. v. Schrütter: Ztschr. f. klin. Med., 1907, lxii, 508.
59. Wagner: München. med. Wchnschr., 1903, l, 133.
60. Watsuji, S.: Ztschr. f. Krebsforsch., Jena, 1903-4, i, 445.
61. Weinberger: Ztschr. f. Heilk., 1901, ii, 78.
62. Werner, M.: Das primäre Lungencarcinom, etc., Dissert., Freiburg, 1891.
63. West: Tr. London Path. Soc., 1884, xxxv, 87.

extends into both upper and lower lobes. Alveolar carcinoma with large polymorphous cells; metastases in spleen, kidneys and brain.

83. Wolf.[3] 1895. M., 58. Epistaxis, dyspnea, dulness over right apex; sputum became bloody; right main bronchus filled with cauliflower growth; left lung very emphysematous. Glandular celled carcinoma; secondaries in lungs, dura mater, nasal septum.

84. Wolf.[3] 1895. M., 55. Mechanic. Bilateral hydrothorax; wall of right main bronchus thickened; bronchiectasis on right. Carcinoma, alveolar in structure; large oval cells; metastases in liver, portal vein, retroperitoneal nodes and seventh and tenth thoracic vertebrae.

85. Wolf.[3] 1895. M., 56. Servant. Dyspnea, weakness, hemoptysis; dulness with bronchial breathing over entire left; left chief bronchus completely filled with tumor invading lower 3 cm. of trachea and constricting right bronchus; emphysema of right lung. Carcinoma, alveolar in structure; secondaries in thyroid and both adrenals. Origin from bronchial glands.

86. Wolf.[3] 1895. M., 67. Collector. Dyspnea, dysphagia, pain in left arm; flatness on percussion over upper left; death from suffocation; left chief bronchus occluded by growth from its own wall. Squamous-celled carcinoma; metastases in pericardium and retroperitoneal lymph-nodes.

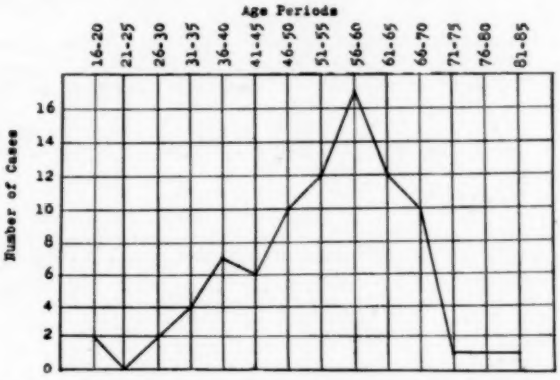

Fig. 5.—The age incidence of primary bronchial carcinomata by five year periods, based on a total of eighty-five cases. The abscissae indicate the number of cases, the ordinates the age periods.

87. Wolf.[3] 1895. M., 69. Mechanic. Clinical picture was that of phthisis; in right chief bronchus, 3 cm. below bifurcation, an oval ulcerated area; bronchiectasis on right. Squamous-celled carcinoma; metastases in bronchial lymph-nodes and liver.

88. Wolf.[3] 1895. M., 54. House porter. Abscess over eighth rib. Squamous-celled carcinoma blocking right main bronchus from bifurcation down, perforating superior vena cava and compressing right innominate; tuberculosis in pleura and right apex; secondaries in both kidneys and left adrenal.

89. Wolf.[3] 1895. M., 65. Mechanic. Clinical picture dominated by cerebral symptoms; tumor mass beneath eroded area in right chief bronchus; bronchiectasis. Squamous-celled carcinoma; metastases in right cerebral cortex and bronchial nodes.

The following case from the Medical Service of the University hospital also belongs in this group.

History.—Male, aged 47 (?), awning-maker. Brought to the hospital in an unconscious condition at 9:30 a. m., November 12, 1911. Only a brief history

could be obtained from the patient's friends. He had not been as well as formerly for two years. Marked dyspnea for some time, with epistaxis and hemoptysis. The patient had believed that he had asthma, and stramonium leaves were found in his pockets. He became unconscious while seated in a chair in a hotel lobby.

Examination.—The following notes are taken from the hospital records: The patient was intensely cyanotic, skin dry, pupils evenly and markedly contracted, reacting but very little to light. There was marked dyspnea, with great activity of the accessory muscles. Respiration characterized by a short deep inspiration and long expiratory period. The rate was but 10 or 12 per minute. There were many râles during inspiration. No area of dulness was detected.

The heart was regular, apparently not enlarged, and the heart sounds were of good quality; the rate, 110. The radial pulse was of good size, quick, and fairly compressible.

The patient moved both arms readily but no spontaneous movements of the legs were noted.

The urine, obtained by catheterization, was negative except for a heavy trace of albumen. Tests for morphin applied to the urine were negative. Stomach washings contained only a little slimy mucus and a few fine particles of food.

The rectal temperature was 97.8 and 96 F.

Treatment.—A coffee and whiskey enema was retained. The stomach was washed with potassium permanganate solution, 1 to 500, and 1/150 gr. doses of atropin administered on the assumption that the case might be one of morphin poisoning. Oxygen was also used, and strychnin in 1/30 gr. doses.

Death occurred at 1:35 p. m. of the same day. Respiration ceased about one minute before the heart stopped beating.

Necropsy.—The autopsy was performed by Dr. A. S. Warthin at 9:00 a. m., Nov. 13, 1911. The more important points in the protocol dictated by Dr. Warthin are included below.

Thorax long; epigastric angle less than a right angle; superficial veins not dilated; a small amount of blood-stained mucus in the mouth.

Skull-cap very thin, otherwise negative; dura adherent all over the convexity; arachnoid slightly thickened; convolutions pale and edematous; section of brain otherwise negative.

No free fluid or gas in peritoneal cavity. Liver in median line two finger-breadths below the ensiform. The diaphragm rises to the level of the fifth rib on the right and the sixth rib on the left.

No free gas or fluid in the thoracic cavity. There are a few small adhesions between the visceral and parietal pleurae, most marked at the right apex where the pleura shows a dense hyaline thickening; no enlarged lymph-nodes in the anterior mediastinum.

Apex of the heart at the sixth interspace in nipple line. Auricles, particularly the right, distended with unclotted blood. Mitral orifice somewhat larger than normal, admitting two fingers with ease; tricuspid admits four fingers; valve flaps negative.

Orifices and valve flaps of pulmonary artery and aorta negative. No narrowing of lumen of aorta and no aneurysm.

Left lung: Anterior border extends to left sternal line. Large bronchi filled with creamy exudate; bronchial nodes small and heavily pigmented; moderately voluminous; marked congestion and edema.

Right lung: Anterior border extends to right sternal line. The lung is bound by many adhesions to a tumor the size of an orange which is connected with the bronchial nodes, the esophagus and the descending aorta. The tumor mass completely surrounds the main bronchus to the right lung and has infiltrated and destroyed the bronchial wall. The lumen of the bronchus is markedly narrowed (Fig. 1). The tumor also extends along the bronchus to the upper lobe.

At the level of the bifurcation the trachea is much stenosed by the pressure of the tumor mass. This stenosis affects the left main bronchus more than the right. The former barely admits a glass rod 2 mm. in diameter. The lumen of

the esophagus is also narrowed at the same level and the wall is firmly attached to the tumor mass.

Spleen: Small; capsule slightly wrinkled and contains numerous small hyaline thickenings; atrophy of pulp and follicles, increase of stroma.

Left kidney: Fibrous capsule strips easily. On section the parenchyma is deep purplish red, bleeds freely. Several small grayish nodules beneath the surface.

Right Kidney: Shows less passive congestion than the left, otherwise similar.

Adrenals: Normal in size: medulla preserved.

Large and Small Intestines: Partially distended with gas; duodenum negative; pylorus patent; stomach mucosa slightly atrophic; no erosions or hemorrhages.

Pancreas: Congested and softer than normal.

Liver: Capsule somewhat thickened and contains small hyaline areas; parenchyma shows a marked acute passive congestion; gall-bladder shows old adhesions.

Abdominal aorta shows patches of sclerosis and atheroma.

Retroperitoneal lymph-nodes are atrophic and congested.

Microscopical Findings.—The most important microscopical findings follow:

Heart: Atrophy; fatty degeneration; arteriosclerosis of coronaries.

Spleen: Atrophy; chronic passive congestion; acute congestion; hyaline thickening of capsule.

Brain: Congestion, edema, chronic leptomeningitis.

Kidneys: Acute passive congestion, atrophy, cloudy swelling, metastatic adenocarcinoma.

Right Lung: Chronic abscess, chronic fibroid pneumonia, bronchiectasis, chronic passive congestion.

Left Lung: Emphysema, chronic passive congestion.

Liver: Atrophy, chronic passive congestion, hyaline areas in capsule are thickenings with hyaline blood-vessels, probably nearly healed angiocavernosa.

Pancreas: Atrophy, sclerosis, post mortem change.

Neoplasm: After formaldehyd fixation and paraffin infiltration, sections of the neoplastic tissues were stained in hematoxylin and eosin, carbol-kresyl-echt-violett, Bismarck brown and hematoxylin and picric acid. The primary tumor mass shows an adenocarcinoma with irregular gland-like spaces (Fig. 2) which are lined by two or more rows of epithelial cells, with large spherical or oval nuclei. There is some tendency for the oval nuclei to be arranged with their long axes parallel to each other and perpendicular to the lumina, giving a marked cylindric-celled appearance. The cell nuclei stain readily but not intensely with the various basic stains. The alveolar spaces are filled with a finely granular material which takes a bluish stain with hematoxylin and reacts metachromatically with carbol-kresyl-echt-violett, thus resembling mucin in every particular.

The same architectural and cell characteristics are found in all parts of the neoplasm examined. In the more peripheral portions of the growth such as the part invading the esophageal wall (Fig. 3) the alveolar spaces are smaller. Even in the metastases in the kidney (Fig. 4) mucin formation has taken place.

The neoplasm must be considered a primary adenocarcinoma of the right main bronchus, cylindric-celled in character, probably arising from the bronchial mucous glands.

GENERAL CONSIDERATIONS

Frequency.—The number of cases reported indicates that bronchial carcinoma is not as rare a disease as has been supposed. Wolf[3] found lung and bronchial carcinomata in .223 per cent. of 20,116 autopsies and Pässler considers 87 per cent. of the neoplasms in this group to be of bronchial origin. The difficulty in diagnosing the condition has done much to keep down the percentage, but now that its frequency of occur-

rence is more fully realized and search is being made for it, the ratio of incidence is being raised. This is shown by the statistics of the combined lung and bronchial group which Adler[1] presents in his monograph. A summation of the more recent statistics gives forty cases in a total of 11,093 autopsies, that is, .36 per cent.

Age.—The age was given in eighty-five of the eighty-nine cases in our own list. The distribution over five-year periods is shown by Figure 5. The maximum number is found in the age period 56 to 60, inclusive, but the possibility of occurrence in very young individuals is emphasized by the cases of Hall and Tribe[22] and of Horn,[29] in which the patients were 17 and 18, respectively.

Sex.—In eighty-seven cases, seventy patients were males and seventeen females. Pässler found the ratio to be fifty males to eighteen females in his list of both lung and bronchial carcinomata. After making due allowance for the usual preponderance of male patients in the hospitals from which many of the cases are derived, it still seems evident that bronchial carcinoma is much more common in males than in females.

Location.—Much stress has been laid on a supposed excess of cases of carcinoma of the right bronchial tree as compared to the left. Reinhard,[64] for instance, reported eighteen lung carcinomata from the right side and nine from the left. This disproportion has been attributed to the larger size and more direct course of the right main bronchus with the thought that it would be subjected to a greater degree of mechanical irritation than the left. Adler,[1] in his combined lung and bronchial list, finds the right side more frequently affected than the left, but thinks that the difference is too small to serve as a basis for a theory. We find the two sides to be involved with approximately equal frequency.

Left side	28 cases
Right side	27 cases
Both sides	14 cases

Etiology.—The data in regard to occupation are too meager to permit the drawing of definite conclusions. The case of Boyd,[9] in a bottle-blower, those of Beck,[7] Georgi,[19] and Wolf[3] in blacksmiths, with Handford's[24] in a collier, may be picked from the twenty-five of known occupation as instances in which opportunity for chronic bronchial irritation is obvious. In discussing the etiology of this group, Wolf[3] mentions luetic scars and ulcerations, but puts the most emphasis on a breaking through of softened pigmented lymph-nodes into the bronchial lumen. He says that the *"Pigmentdurchbrüche"* occur especially in the chief bronchi just below the bifurcation and more often on the right side than on the left. This theory has not been supported by the microscopical

64. Reinhard, W.: Arch. d. Heilk., 1878, xix, 369.

findings in subsequent cases, and the part played by dust inhalation requires further study. A very suggestive fact is the preponderance of cases in males who, through occupation and the use of tobacco, are more exposed to the inhalation of irritating substances than are females (Adler[1]).

In but three cases was the disease attributed to trauma. Two of these were from falling (Hinterstoissen[27] and Handford[24]), and the other from a blow on the chest from a piece of iron (Georgi[19]). We may, therefore, be certain that gross trauma is not an important etiological factor.

In a very few instances squamous-celled carcinomata have been described as developing in the walls of bronchiectatic or tuberculous cavities (Kaufmann[67]). The series of cases here reviewed indicates, however, that bronchiectasis is a result rather than a cause of the neoplastic growth. Bronchiectasis is specifically mentioned in fifteen of the case reports, but it occurs in the peripheral portions of the lung rather than at the site of the tumor, and is usually accompanied by atelectasis. It must be considered as due to the stenosis of the bronchus and the inflammatory changes in the lung parenchyma.

In eleven cases out of the eighty-nine a coincident tuberculosis is mentioned. This is usually apical and in two or three instances is spoken of as "old" or "healed." There is nothing to indicate that the tuberculosis was in any way a direct causal factor. It would rather seem that some chronic inflammatory process in the lungs such as tuberculosis, chronic bronchitis or chronic pneumonia, which is also rather frequently found in these histories, may be indirectly the inciting influence. More complete histories of the previous condition of the patient must be had before the importance of these factors can be fully established.

Point of Origin.—Primary carcinoma of the bronchi may arise either from the bronchial mucosa or from the epithelium of the bronchial mucous glands. Analysis of the cases listed gives the following results:

Origin from mucous glands	22
Origin from bronchial mucosa	17
Uncertain or unspecified	50

Of the adenocarcinomata, eighteen are referred to a glandular origin and six to the mucosa. All of the squamous-celled type, in which the point of origin is given, are said to have arisen from the mucosa. In the latter case, there is much in favor of the theory that the malignant change is associated with a metaplasia of the surface epithelium to the squamous type. The case of Davis and Le Count is illustrative, for the mucosa was found to resemble skin from a centimeter above the tracheal bifurcation to a point some distance along each of the main bronchi.

67. Kaufmann: Lehrbuch der Speziellen Pathologischen Anatomie, p. 303.

Von Schrötter[58] also argues for a metaplastic origin for the squamous-celled type rather than referring it to an embryonal anlage.

In the case here reported the origin was probably from the mucous glands. As in many other neoplasms of similar character, the *"Uebergangsbilder,"* which would prove this point, are lacking. However, many sections taken along the main bronchus show small islands of tumor, occupying the normal position of mucous glands, equaling normal mucous glands in size, and themselves containing mucus. At this same point the bronchial mucosa is inflamed and eroded, but nowhere neoplastic. The general architecture of the tumor is also very suggestive of the glandular origin.

Histopathology.—In fifty-five cases, the general structural character of the neoplasm is given. It is spoken of as

Alveolar, acinar or adenomatous	in 45 cases
Medullary	in 5 cases
Scirrhous	in 3 cases
Simplex	in 2 cases

This shows an unduly large number of the first group, for in most of the cases described as "squamous," nothing is said in regard to structure. According to cell type, we find these carcinomata described as

Squamous celled in	25 cases
Cylindric celled in	18 cases
Polymorphous celled in	10 cases
Round or oval celled in	2 cases
Gland celled in	1 case
Cuboidal celled in	1 case

It is probable that most of the cases in the last four groups might have been placed in one or the other of the first two. The two chief forms of bronchial carcinomata are, therefore, the adenomatous cylindric-celled type and the squamous-celled type.

As has been described, mucus formation was a prominent feature in the histological picture of our own case. It is mentioned in ten of those listed, all adenomatous in character. The extent of mucus production varies from the formation of intracellular vacuoles, as in the case of Beck,[7] to the filling of large alveoli with metachromatically staining mucin, as in the cases of Stropeni[56] and Dömeny.[12] Boecker[8] and Horn[29] consider that mucus formation does not prove an origin from the bronchial mucous glands, although in most of the other cases such an origin is maintained. Mucus formation in the metastases has been noted in three cases, including our own.

Metastases.—The proneness of lung and bronchial carcinomata to give rise to metastases has been much emphasized. Wolf[3] found secondaries in twenty-one cases out of twenty-three; Pässler,[5] in sixty-three

cases out of seventy-four. The figures from our list of exclusively bronchial carcinomata closely parallel these.

Metastases found to be present	70 cases
Metastases not mentioned	11 cases
Metastases not found	9 cases

The locations of the secondary growths were the most varied. Some unusual sites are mentioned, such as in the finger (Hinterstoissen[37]), and nasal septum (Wolf[3]). It is unnecessary to give a complete enumeration of the secondaries found, but the bronchial, cervical and axillary lymph-nodes, liver, kidneys and adrenals were most frequently involved. In the case here reported, the only secondaries were those found in the kidney. Two other observations should be mentioned.

1. The proneness to brain metastases, which are found in twelve cases. The clinical picture may be dominated by such secondaries. Dömeny[12] reports a case in which the chief findings were pain in the head, visual and auditory disturbances and choked disk. In this instance there were seven brain metastases from a bronchial adenocarcinoma.

2. The frequent occurrence of palpable secondaries in the lymph-nodes. In thirteen cases such nodes were noted, usually cervical, supraclavicular or axillary. The reported cases show that, as a rule, if the glands of but one side are invaded the neoplasm will be found to involve the bronchus of the same side.

SYMPTOMATOLOGY AND DIAGNOSIS

In a few cases an ante mortem diagnosis of bronchial carcinoma is absolutely impossible. Such cases fall into three groups: (1) those in which the neoplasm is very small and is discovered only incidentally, as in the case reported by Klüber;[33] (2) those in which the clinical picture is dominated by cerebral or other metastases, as in one of Wolf's cases; (3) those in which the patients are practically moribund when first seen. The case here reported falls in the last group.

On the other hand, diagnosis is often possible, as is shown by the fact that in about ten of the cases listed in this paper the nature of the process was ascertained before necropsy. With the additional aids now available the proportion of diagnosed cases should be very much increased.

The chief symptoms mentioned in the clinical histories of the listed cases, in the order of their frequency, are as follows:

1. *Cough.*—Sometimes this is spoken of as a "dry" cough, but the case reports give no characteristic description.

2. *Dyspnea.*—This very frequent symptom is usually progressive in character, becoming more and more severe, and oftentimes terminating in the death of the patient in a suffocative attack.

3. *Hemoptysis.*—Hemorrhage, ranging from a bloody streak in an otherwise mucopurulent sputum to a brisk flow of bright red blood, is one of the most common findings. In forty-two cases in which the character of the sputum is mentioned, there was some degree of hemoptysis in thirty-five. The "black-currant jelly" or "raspberry jelly" sputum once thought to be characteristic of lung and bronchial carcinomata is rarely mentioned in case reports.

4. *Pain.*—Pain is also frequently a factor in the clinical picture. It is felt in the chest, usually on the affected side, or in that shoulder and arm. Here it may be explained as a referred pain, or it may be due to pressure on the brachial plexus from a secondary involvement of axillary or clavicular nodes.

5. *Pressure Symptoms.*—The group of symptoms arising from pressure of the neoplasm on surrounding structures is of great diagnostic value. From obstruction to the venous return we have dilatation of the superficial veins of head and thorax, often accompanied by edema. These changes are mentioned in nine cases. In five paralysis of the recurrent laryngeal is noted and two others showed aphonia. Dysphagia is reported in four instances, and in one pupillary inequality and ptosis of one lid developed.

The usual absence of fever and night sweats from the symptom complex is worthy of note. In but four of the ninety cases is fever mentioned.

The physical findings vary with the extent of the neoplasm, with the degree of stenosis of the bronchi and with complicating lung conditions. The usual percussion findings are dulness in the lobe or lobes supplied by the affected bronchus and hyperresonance in the opposite lung. The dulness depends largely on atelectasis due to air absorption from the alveoli of the lobes of which the bronchi have been blocked. The hyperresonance is due to a compensatory emphysema in the opposite lung. Signs of cavitation in the affected lung are also frequently found. In the bronchial type of pulmonary carcinoma cavity formation is usually due to bronchiectasis rather than to breaking down of the neoplasm, a process to which it is often erroneously referred. As previously mentioned, bronchiectasis is practically always found in the portion of the bronchial tree beyond the stenosis. In general, it may be said that the physical findings in bronchial carcinoma are those of bronchial obstruction.

Bronchoscopic examination may confirm a diagnosis of bronchial carcinoma. Rénon, Géraudel and Marre[65] report such a case (not included in list through lack of autopsy findings), in which the lower portion of the left main bronchus was seen to be entirely obstructed by a neoplastic growth. A piece of the tumor was removed through the bronchoscope, examined microscopically, and found to be squamous-celled in character.

65. Rénon, L.: Géraudel et Marre. Presse méd., Paris, 1910, xviii, 401.

Radioscopy is of the greatest service in these cases. After describing thirteen cases of lung and bronchial carcinoma which were examined radioscopically, Otten[66] concludes that tumors arising from a large bronchus at the hilus and spreading into the lung as a compact mass, should give little difficulty; that differentiation is difficult when the neoplasm spreads diffusely along the bronchial tree, and that the skiagram gives the most certain information of any method in regard to the precise localization, the manner of spreading and the extent of bronchial neoplasms.

No opportunity should be lost to obtain evidence in regard to the histological character of the neoplasm. This may often be accomplished by the excision of a metastatic growth, as previously mentioned; by removal of a specimen through the bronchoscope, or by careful search of the sputum. The atypical cells were recognized in the sputum in four of the cases in our list. Stropeni[56] said that no symptom was pathognostic except the finding of tumor cells in the sputum, but now bronchoscopic examination and removal of a specimen may be added as an even more satisfactory procedure.

Treatment.—In the past the diagnosis of bronchial carcinoma has been considered as chiefly of prognostic value. However, in the rapid advance in intrathoracic surgery the condition is becoming an operable one. Ders[68] reports a total resection of a carcinomatous lung, in which case the death of the patient resulted from a septic process developing in the lung stump. In Lenhartz'[69] group of cases a resection of a carcinomatous lobe is reported in which the patient remained comparatively well one and a half years after the operation. Küttner[70] and Sauerbruch[70] have also removed large sections of carcinomatous lungs with success. The early diagnosis of this condition therefore becomes a matter of the greatest importance, for only through an early diagnosis can the patient be offered any hope of relief or cure. With this in view, bronchial carcinoma should always be considered a possibility in diagnosing lung conditions. Patients with cough, dyspnea, hemoptysis or pressure symptoms in various combinations of intensity should be studied by the newer diagnostic methods which have been applied to this condition. In doubtful cases, Adler[1] advises an exploratory thoracotomy.

Modern lung surgery furnishes the greatest incentive for the early diagnosis of bronchial carcinoma, and it is hoped that this study will aid in making such diagnoses possible.

I wish to acknowledge my gratitude to Dr. A. S. Warthin for his supervision and assistance in the preparation of this study.

66. Otten, M.: Fortschr. a. d. Geb. d. Röntgenstrahlen, Hamburg, 1906, ix, 369.
68. Ders: Centralbl. f. Chir., 1911, xxxviii, 427.
69. Lenhartz: Cited by Brauer, Centralbl. f. Chir., 1911, xxxviii, 427.
70. Küttner, Sauerbruch: Cited by Batzdorff. Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1912, xxi, p. 1.

THE LOCALIZATION OF IMPULSE INITIATION AND CONDUCTION IN THE HEART*

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INTRODUCTION

It has ever and quite naturally been true that the discovery of a new structure immediately has started an effort on the part of investigators to determine the function thereof, and conversely that the discovery of a new function or property has initiated an effort to discover some structure that could be made the seat of such function or property.

The history of the localization of impulse initiation and impulse conduction in the heart illustrates in a striking manner these tendencies and their effects. The heart is spontaneously rhythmical. Does it contain a definite structure whose purpose it is to initiate this spontaneous rhythm? Or, again, in the heart, impulses are carried from one part to another. Is this the function of a special structure? Conversely, a structure is found in the heart which conceivably might act as pace-maker, while still another is found which might well serve to carry the excitation waves from point to point in the heart. At once experiments are devised with the object of obtaining answers to these questions. Nothing could be more logical, nor in the long run more certain of gaining the goal than such a course. Nevertheless there is a danger, very well illustrated by the history of these subjects, of accepting the bare inference in either direction as a fact, or of accepting as conclusive experiments which by the investigators themselves are regarded only as suggestive, or, owing to the reasonableness of the inference, there even is a danger that the investigators themselves may be led to draw conclusions from evidence which at the time is obviously insufficient, or which time may show to have been insufficient.

While the main purpose of this paper is to review critically the work that has been done in the effort to localize the functions of impulse initiation and conduction in the heart, it is hoped that it will at the same time serve to illuminate the way to some of the pitfalls and dangers and difficulties that beset investigators in this field of physiology.

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I. THE LOCALIZATION OF IMPULSE INITIATION

HISTORICAL

The earliest attempt to account for the regularity of the heart's action led the older physiologists into all sorts of futile hypotheses. Down to the year 1813 the term *"organic instinct"* was employed to designate it.[1] Long before this date, however, physiologists were in the possession of facts which might have sufficed for a generalization closely approximating the truth as we now see it. Thus Harvey and some of the older anatomists observed the movements of the venae cavae to continue in some of the lower animals after the auricles had ceased to move. In the search for the *ultimum mòriens* of the body, Haller, and perhaps others before him, discovered that in cold-blooded animals the right auricle usually survives death of the organism longer than other parts of the heart. This survival, however, was not attributed to any property of the tissue of the heart, but was thought to be due to the fact that after death the right side of the heart generally contains a greater or less quantity of blood which was supposed, in the time of Haller, to supply the stimulus to the heart.

Much later, in 1811, Nysten was able to confirm Haller from a study of the human species after decapitation by the guillotine. Nysten, indeed, went one step farther; he studied the irritability of various regions of the human heart, using galvanism as the stimulant and found that usually "those parts of the auricle around the entrance of the venae cavae retain their contractility longest."

The sequence of the heart beat in both warm- and cold-blooded animals was also known at this time. But rather than refer this sequence to any definite structure in the heart and possibly under the influence of the iatromechanists, mechanical rather than physiological explanations of the orderliness of the contractions were sought. For instance, according to Haller and Senac, the usual sequence of the several chambers is exactly what one would expect if the blood is the "habitual stimulant on which the movements of the heart depend." In view of the fact that the contraction of the heart occurs in the order in which the blood flows into its different cavities, this conclusion seemed quite satisfactory. The regular sequence of the auricles and ventricles of the empty heart was attributed by Reid,[1] in 1839, to mechanical stimulation of the empty ventricle by the tug of the auricles. Although Reid apparently was not able to free himself entirely of the influence of the prevailing hypotheses, he, nevertheless, records an experiment which led him to suggest in a vague fashion another possible explanation of the sequence of beat. He discovered that an empty heart would beat when all stimuli were removed

1. Reid: In Todd's Encyclopedia of Anatomy and Physiology, London, 1839, p. 607.

by placing it in the exhausted receiver of an air pump, and concluded that "we are almost obliged to have recourse to the supposition that there is some innate power in the heart itself."

As an example of another type of mechanical explanation of the transmission of the impulse along the heart may be mentioned here in passing one suggested by Kürschner[2] in 1850. Kürschner ventured to suggest that the valve musculature, which is described in the second part of this paper, by pulling on the ventricles, and thus putting into motion a complex mechanism, determines the sequence of the auricles and ventricles.

The experiment of Stannius, described in 1852, has done more, however, toward putting physiologists on the right track than any other contribution to this subject. Stannius, it is well known, separated by means of a ligature the sinus from the auricles in the frog's heart and found that the sinus then continued to beat with undisturbed rate, whereas the subjacent parts of the heart came to rest. It was this experiment, as interpreted and built upon by Gaskell, Englemann and others, forty or more years later, that finally led to the conception that the pace-maker is a part of the heart itself, and that part, namely, the sinus region, which possesses the highest grade of rhythmicity. Before this conclusion was generally accepted, however, the view had first to be overcome that the beat of the heart is dependent on the ganglia, described by Remak shortly before Stannius reported the results of his ligature of the heart. It was Gaskell who showed that in the frog's heart rhythmicity is not located in the ganglia, but "in those parts of the heart muscle which remain least altered both in circular arrangement of their fibers and in their physiological status."

We may be permitted to recall in this connection a recently closed chapter in the physiology of the heart, because it illustrates so well the pitfalls in the path of our efforts to attach function to a likely structure. Kaiser,[3] in 1894, reported that if the frog's heart is brought to a standstill by tying off the sinus, a single stimulus applied to the surface of either the auricle or the ventricle is followed by only a single response; whereas if the stimulus be applied in the region of Bidder's ganglion in the auriculoventricular ring, each single stimulation is followed by a series of rhythmical contractions. He then goes on to say that "if Bidder's ganglion be removed, stimulation in the region which before aroused a series of responses now gives only one response for each stimulus." Kaiser, therefore, regarded the ganglion as the rhythmical center of the heart. Gaskell has shown since, however, that Kaiser's

2. Kürschner: Wagner's Handwörterbuch der Physiologie, Braunschweig, 1850, p. 80.

3. Kaiser: See Martin, Bull. Johns Hopkins Hosp., 1905, xvi, 380.

conclusions were based on faulty experimentation. By working more carefully, Gaskell proved that Bidder's ganglion might be pierced with a needle without causing any contractions of the heart; whereas the slightest prick of the muscular tissue in the auriculoventricular groove would give rise to a series of contractions. Obviously Kaiser had stimulated the heart tissue subjacent to the ganglion, though he believed he was stimulating the ganglion only. It is hoped that subsequent sections of this paper will serve to show how closely akin to this problem and to the methods of solving it, is the problem of impulse initiation as it presents itself to us to-day.

ANATOMICAL

The recent impetus given to the attempts to localize a pace-maker of the heart is perhaps due more to certain recent advances in the anatomy of the heart than to any other one cause, and we must, therefore, first direct attention to the light which has been shed on our subject by the efforts of anatomists.

Of the primitive hearts, that of the eel is selected as a type, owing to the care with which its physiology has been studied, and because it seems to elucidate especially well some of the problems with which this paper deals. This heart[4] comprises three contractile cavities, the sinus venosus, the auricle and the ventricle. The arrangement and relations of these chambers are shown only diagrammatically in Figure 1. At the junction of the sinus with the auricle the whole circumference of the sinus wall does not terminate directly in the proper auricular tissue, for here the proper auricular tissue does not form a complete chamber, its floor being made up of what appears to be a direct prolongation of the ventral wall of the sinus. The auricle is not directly continuous with the ventricle; there is a short intervening tubular communication resembling the canalis auricularis. This connection is effected by means of an extremely narrow and prolonged strand of muscle fibers which is prolonged from the muscular wall of the auricular canal, and, penetrating a considerable amount of connective tissue which lies in that situation, at length becomes continuous with the muscular substance of the ventricle. The mucular continuity between the canalis and the ventricle is established by means of a remarkably long and slender isthmus of muscle substance which becomes continuous with the central fibers of the ventricle. In an effort to show the relation of the mammalian heart to that of the eel, Figure 2 has been evolved. We do not mean to maintain that the assumptions involved in this diagram would pass muster before a comparative anatomist. Be that as it may, the diagram has proved of great

4. McWilliam: Jour. Physiol., 1885, vi, 192, from which what follows is largely quoted.

service in the attempt to unify the contributions to the subject of impulse initiation and conduction.

Inasmuch as the sinus is the pace-maker of the cold-blooded heart, it behooves us first to determine what becomes of the sinus in the evolution of the heart to the mammalian form. The embryological method of determining this matter has been pursued by His.[5] His investigations have shown that in the course of development the counterpart of the sinus venosus of the cold-blooded heart becomes in the human heart the part of the right auricle which His designates the sinus reuniens.[6] One portion of the sinus, namely, the coronary sinus, according to His, persists as an easily distinguishable structure; the right horn of the sinus, however, sinks deep into the auricle, and the walls of these two

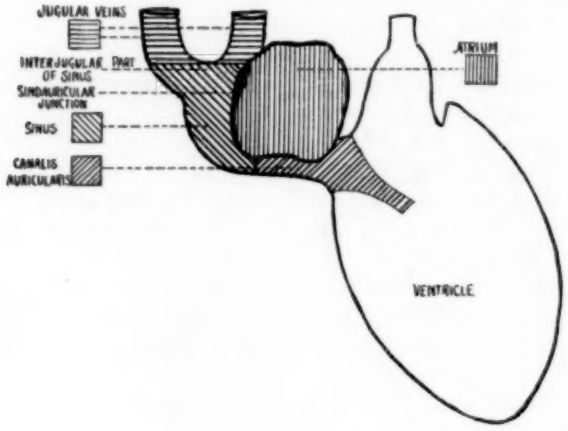

FIGURE 1

Fig. 1.—Heart of the eel. Diagrammatic. Modified from McWilliam.

regions become fused to such an extent that anatomists, to quote, "as yet have had no occasion to designate the sinus as a definite part of the heart." Nevertheless, its limits are distinguishable at all ages. Externally it is delimited on the right by the sulcus terminalis, a groove on the surface of the heart just to the right of the opening into the auricles of the superior and inferior venae cavae. On the inner surface of the auricle corresponding with the sulcus terminalis is a ridge, the tenia terminalis. To the right of this ridge the wall of the auricle is roughened by the pectinate muscle; to the left it is smooth. This smooth part is the

5. His: Anatomie menschlicher Embryonen, Leipzig, 1880, p. 148.

6. The terms sinus reuniens and sinus venosus will be employed interchangeably.

region of the sinus reuniens. By the comparative anatomical path as pursued by Keith and Flack,[7] the sinus in the adult mammalian heart has been found to have practically the same contour. These investigators also state that in the mammalian heart the greater part of the sinus is submerged by an overgrowth of muscular tissue of other regions. According to Keith and Flack, "two parts only are left exposed on the surface of the heart: (1) the musculature of the superior vena cava, (2) the musculature of the coronary sinus."

We may therefore conclude that in the mammalian heart the remnants of the sinus venosus are to be found in an extensive area of the right auricle. Roughly, this area may be said to occupy the region between and including the superior vena cava above and the coronary

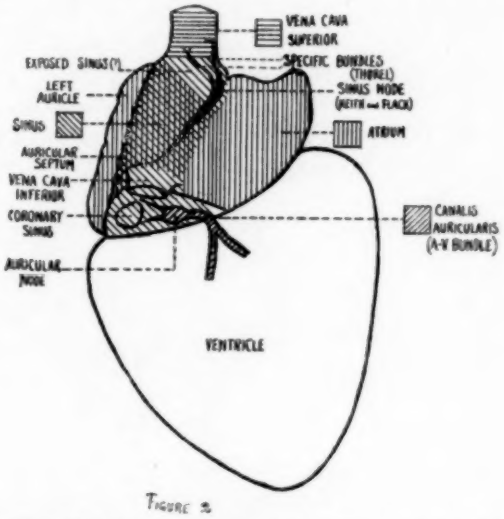

FIGURE 2

Fig. 2.—Mammalian heart. Diagrammatic. Figures 1 and 2 are drawn to show schematically the probable homologies of the cold-blooded and warm-blooded hearts.

sinus below, and extending from this region to the insertion of the interauricular septum into the auriculoventricular junction (Fig. 2). The amount of sinus tissue persisting is not made clear; presumably but little remains.

In the same paper, Keith and Flack describe the structure now known as the sinus node or the node of Keith and Flack. This node, owing largely to the suggestion thrown out by Keith and Flack to the effect that in it "the dominating rhythm of the heart normally begins," has since assumed great prominence in the literature of the subject of impulse

7. Keith and Flack: Jour. Anat. and Physiol., 1907, xli, 172.

initiation, whole volumes having already been written on it. Originally described as "numerous peculiar muscle fibers, some nerve cells and nerve fibers" surrounding the artery lying in the sinoauricular junction and located in the groove termed by His the sulcus terminalis, this node, or perhaps, the so-called specialized tissue of this region, has with further investigation assumed a more definite form, and what is of greater significance in the interpretation of the results of experimentation, has grown in extent and complexity. Thus Koch[8] has shown that it is club-shaped, a distinct enlargement, known as the head, sending a few fine strands back into the angle between the superior cava and the right auricular appendix, and a long tapering process downward to terminate midway between the superior and inferior cavae (Fig. 2). Thorel,[9] on the other hand, described not alone a structure of this form, but in addition many strands beginning as loops around the superior cava, and extending downward as far as the coronary sinus (Fig. 2). The fibers of the node communicate freely with the heart muscle fibers that surround it. It is important to bear in mind that the sinus node is not the sinus venosus, but is a so-called specialized tissue lying in the sino-auricular junction.

Although the discussion of the anatomy of the auriculoventricular bundle is reserved for the second part of this paper, it is necessary to state here that this structure is now believed to be a remnant of the part of the primitive heart-tube, known as the canalis auricularis, which unites the sinus venosus with the ventricle. It consequently should be termed the sinoventricular instead of the auriculoventricular bundle.

PHYSIOLOGICAL SECTION

GENERAL LOCALIZATION IN THE MAMMALIAN HEART

In the past the study of the heart beat in cold-blooded animals has been of inestimable service in the elucidation of the functions of the warm-blooded heart. Experience of many years has shown that practically all of the findings obtained from the study of the former can be applied with but slight modification to the latter. Such knowledge of the site of normal impulse initiation as we have gained from observation of the cold-blooded heart should, therefore, be of service to those who are now concerned with this problem as it applies to the warm-blooded heart. In cold-blooded animals the beat starts in the great veins above the point where they unite with the sinus venosus, or if not there, certainly not below the sinus venosus.[10] In view of the picture by Keith

8. Koch: Med. Klin., 1911, No. 12.

9. Thorel: Verhandl. d. deutsch. path. Gesellsch., 1910, p. 71.

10. Meek and Eyster: Am. Jour. Physiol., 1912, xxxi, 31.

and Flack indicating that in the turtle's heart there is at the sinoauricular junction a collection of tissue which closely resembles the sinus node of higher animals and seems to be its homologue, we wish to lay special stress on the fact that the beat of the turtle's heart does not begin in the sinoauricular junction. Just what becomes of the great veins in the evolution of the heart has not, so far as I am aware, been determined. Presumably they become incorporated with the sinus in the wall of the right auricle. We should, therefore, expect the beat of the mammalian heart to begin in the right auricle in the region of the sinus venosus, or in the veins opening into it; not at the sinoauricular junction.

RHYTHMICITY OF THE RIGHT AURICLE

Attention has already been called to the observation of Nysten to the effect that the right auricle is the part of the heart of man that longest preserves its irritability to the constant current, and that for a long time this region was known to be the *ultimum moriens* of the body. That the right auricle is the most rhythmical part of the mammalian heart can be demonstrated in a striking manner by severing functionally the right auricle from the rest of the heart, but leaving its nutritive connection with the heart for the most part undisturbed. When this is done the right auricle invariably beats more rapidly than the rest of the heart.[11] When the functional separation is not quite complete a partial block may develop, every other or every third beat of the right auricle determining a beat of the rest of the heart.[12] It is of interest in this connection that the left auricle, when severed from the rest of the heart by the same method, usually ceases to beat at once and definitively. It is therefore obvious that the part of the heart in which the sinus venosus lies buried, normally determines the beat of the heart.

EXACT LOCALIZATION IN MAMMALIAN HEART

GENERAL REMARKS

In considering the efforts directed toward a more exact localization of the site of impulse initiation reference may at once be made to the view, which now is widely considered a demonstrated fact,[13] that the sinus node of Keith and Flack is the normal pace-maker of the heart. At the very beginning of the discussion of this subject we wish to call attention again to certain *a priori* considerations that are opposed to this view. The sinus node lies in the sinoauricular junction; if it is

11. Fredericq: Acad. roy. de Belg. Bull. de la cl. sc., 1901, p. 126; ref. Arch. internat. de physiol., 1912, xii, 109; Erlanger and Blackman: Am. Jour. Physiol., 1907, xix, 125.

12. Erlanger and Blackman: Am. Jour. Physiol., 1907, xix, 125.

13. See, for example, Howell, Text-Book of Physiology, Phila., 1911, Ed. 4, p. 529.

the pace-maker it would therefore follow that in the mammalian heart the beat begins in this junction. This, we have seen, is not the case in lower forms. It should be borne in mind, however, that the last word has not yet been said with regard to the anatomy, or better perhaps with regard to the homologies of the sinus node. According to Koch's latest description, the node in the dog is two or more centimeters long, while Thorel claims that the so-called specialized tissue of this region is not confined to the sinus node of Keith and Flack, but occurs in a rather extensive area; an area, it would seem, that is almost coterminal with the sinus region (Fig. 2). If the latter view should prove to be correct, then to say that impulse initiation is localized in the specialized tissue is tantamount to saying that it is localized in the sinus. However this may be, in the attempts to determine whether or not the sinus node is the normal pace-maker, practically all investigators have had before them the node as pictured by Koch.

INSPECTION

The first effort toward a more exact localization of impulse initiation in the warm-blooded heart was made by McWilliam[14] in 1888. McWilliam observed that, in the dying heart, spontaneous contractions begin either just at the point of union of the great veins with the heart, or in the wall of the veins a short distance above this point. The same method of observation in the hands of other investigators has yielded a somewhat similar result. Thus in the dying heart of the rabbit, Hering[15] found that contraction waves may start in the region of the mouths of the two superior cavae, and in the dog's heart[16] usually at the mouth of the superior vena cava; occasionally, however, at the mouth of the inferior vena cava. Fredericq[17] finds that in the dog the impulse starts in the right auricle between the two cavae. I have often watched for the spot from which the last or the first impulse starts in the dying or reviving heart, respectively, of mammals,[12] but have never succeeded in making a finer localization than to the region of the great veins as a whole. Finally Koch has concluded from observations on the hearts of still-born human fetuses that the beat starts in the coronary sinus. It is, therefore, obvious that inspection of the heart certainly locates the site of impulse initiation in the region of the sinus venosus, possibly nearer to the superior than to the inferior cava. A finer localization by this method does not seem to be possible. It should be borne in mind, however, that the logic of this method of determining the normal cardiomotor area is not entirely clear. It serves to locate the most viable parts

14. McWilliam: Jour. Physiol., 1888, ix, 167.
15. Hering: Pflüger's Arch. f. d. ges. Physiol., 1900, lxxxii, 21.
16. Hering: München. med. Wchnschr., 1909, lvi, 845.
17. Fredericq: Arch. internat. de physiol., 1906, iv, 60.

of the heart, not those possessing the highest rate of rhythm, which, after all has been said, is *the* property that determines the seat of origin of the contraction wave.

RHYTHMICITY OF DIFFERENT REGIONS OF THE RIGHT AURICLE AS DETERMINED BY EXCISION AND BY STRIPS

The above-mentioned experiments show that the most highly rhythmical portion of the heart is the right auricle. Are all parts of this region equally rhythmical, or are certain parts more rhythmical than others? By excising in various ways various parts of the auricles of the perfused cat's heart and noting the effect on the heart rate, it was shown[12] in 1907 that the region of the great veins probably possesses the highest grade of rhythmicity, but that the rhythm of this region exceeds but little that of the coronary sinus region. It was pointed out, however, that this method is open to the objection that the cuts, by altering the distribution of the perfusion fluid to the several parts of the auricles, might have altered the rhythmicity of neighboring parts. Three years later it was discovered that strips of the cat's, rabbit's and dog's auricle, when excised, placed in a bath of Locke's solution, and occasionally stimulated tetanically, would give a beautiful series of beats, and for hours, provided, however, that the strips contained tissue from that region of the right auricle which approximately coincides with the sinus reuniens of His.[18] These experiments furnish further evidence in favor of the view that the beat is initiated in the sinus region. But what is of greater significance to the present discussion is the observation made by the aid of this method that the regions of the superior vena cava, of the inferior vena cava and of the coronary sinus possess approximately the same grade of rhythmicity. Within the last few months this observation has been completely confirmed by Moorhouse,[19] who, in addition, has controlled his experiments by exactly localizing the sinus node by means of serial sections. His experiments show in a striking manner that a strip containing the sinus node as compared with strips made from the auricle just below the node or just posterior to the node, is far from exhibiting a constant predominance of rate.

Furthermore, it has been found that stimulation of auricular strips frequently is followed by an acceleration of the rate of their beat.[12] Such an acceleration is obtained, however, only when the part of the strip stimulated is from the sinus region of the heart. In their analyses of the functions of the various parts of the cold-blooded heart, Gaskell, Engelmann, McWilliam and others, lay the greatest stress on this reaction of heart muscle to stimulation, maintaining that it is characteristic

18. Erlanger: Am. Jour. Physiol., 1910, xxvii, 87.
19. Moorhouse: Am. Jour. Physiol., 1912, xxx, 358.

of highly rhythmical tissues. However this may be, it cannot be without interest that in the mammalian heart this response is obtained, not alone from the region of the sinus node, but from the whole of the sinus region.

EVIDENCE FURNISHED BY ACTION OF DRUGS ON STRIPS

Inasmuch as a great deal of stress is laid in this paper on evidence furnished by strips of the auricles beating in Locke's solution, it is of prime importance to prove that such evidence is valid. In the case of the cold-blooded heart, strips have for many years been employed for the purpose of determining the properties of the various parts of the heart, and of interpreting the response of the heart to stimuli of all kinds. So far as I am aware, all of the material thus obtained has been accepted by physiologists without question as applying to the whole heart. Nevertheless we must be prepared to show that mammalian strips do react as does normal heart muscle. Moorhouse is now engaged in an effort to gather evidence bearing on this question. His main method is to study the behavior of strips when bathed in Locke's solution to which various of the so-called heart drugs are from time to time added. Although this research is not yet completed, it has proceeded far enough to justify the statement that the strips containing sinus tissue respond exactly as does the whole heart to drugs which are supposed to act on muscle tissue as well as on the nervous tissue. Of the latter group, nicotin, which is supposed first to stimulate and then to paralyze the terminals of preganglionic fibers (inhibitory fibers here) first inhibits and subsequently accelerates the strips just as it does the whole isolated heart. Pilocarpin, which slows the whole heart presumably by stimulating the vagus terminals in the heart muscle, also slows the strips, and this action can be prevented as in the whole heart by atropin. Atropin given alone causes the well-known acceleration by paralyzing the vagus terminals, and epinephrin causes the usual acceleration, presumably by stimulating the accelerator terminals in the muscle. Of the drugs whose prime action presumably is on muscular tissue, all that have been tried, namely, caffein, the digitalis group and aconite, increase the rate of the beat and the tone of strips as well as of the whole heart. There can be no doubt, therefore, that the auricular strips behave like perfectly normal intact auricles.

Great emphasis has been laid by all writers who have dealt with the histology of the nodes, on the presence in them of what is termed *specialized* tissue. The nodes have peculiar histological characteristics, which are designated "embryonic." It is assumed by many of these writers that "embryonic" tissue is more rhythmical than other heart tissue, and that consequently the nodes are the motor centers of the heart. Now to come to the point, if this tissue is specialized in the direction of rhythmicity, the sinus node, or the strip containing it,

should not alone be more rhythmical than companion strips containing no nodal tissue, which we have seen is not the case, but in addition it should show a *specialized* response to the heart drugs. It has been found by Moorhouse, however, that if there is any difference at all in the behavior of the strips toward the drugs above mentioned, it is in the direction of greater rhythmicity on the part of the companion sinus strips, not the nodal strip. We may, therefore, conclude with the statement that if it should eventually be proved that the sinus node is the motor center of the heart it would not have this function by virtue of its rhythmical properties.

SIGNIFICANCE OF SLOWING AND STOPPAGE FROM EXCISION OF THE SINUS REUNIENS

Another method extensively employed in the effort to localize the pace-maker of the heart has been to determine whether or not there is a definite and fixed area, excision of which invariably stops the heart, or permanently slows its rate. The interesting results that this method has yielded have usually been applied to the problem in hand without bearing in mind all of the possibilities in the case. It is appreciated that the most plausible explanation of loss of activity following removal of a part of an organ is that the part removed determines that activity. Nevertheless, this is by no means the only explanation; it is conceivable, for instance, that such a removal may result in the establishment of a block between a region of high and of low rhythmicity under which circumstances the latter region, as is well known, will temporarily stop beating and then, after the awakening of its inherent rhythmicity, begin to beat again, though more slowly than before. It is also conceivable that as a result of injury or of partial removal, the function of the parts remaining may be altered or annulled temporarily for reasons that at present are not entirely clear. The central nervous system offers interesting and familiar examples of temporary loss of activity in parts not directly injured or removed. Thus, immediately after the onset of hemiplegia, all of the underlying reflexes are abolished, the paralysis is flaccid; soon, however, the reflexes return and the paralysis then becomes spastic.

The heart itself offers a familiar instance of the wide-spread, and at present inexplicable, effect of local injury or stimulation. It is a well-known fact that momentary stimulation of any point on the auricles or on the ventricles may throw the whole of the corresponding chambers into fibrillation. It has been shown by Garrey[20] that this continued incoordination is not due to any influence emanating primarily from the site stimulated. For if the area that was stimulated be excised while

20. Verbal communication.

fibrillation is continuing, the incoordination of the heart does not stop; whereas the area excised, namely, the one that was stimulated, may at once cease to fibrillate.

With this analysis in mind we may review first the results on the rate of the heart beat of excision of the sinus region and of the sinus node. Excision of the whole sinus region is in effect the first ligature of Stannius, by which the sinus of the frog's heart is functionally separated from the rest of the heart. In this experiment, it will be recalled, the sinus continues to beat, whereas the subjacent parts cease beating for some time. When eventually the distal parts begin to beat it is usually with normal sequence and a slow rate. It is obvious that, owing to the complete fusion of the sinus with the auricle, the exact repetition of this experiment is not possible in mammals. For to remove all sinus tissue would involve removing practically all of the right auricle, with the exception of the appendix and neighboring tissue, down to and including the beginning of the auriculoventricular bundle. The Stannius experiment has, however, been approximated in mammals. In 1907 it was shown[11, 12] that in the dog's heart *in situ* clamping off of all of the region of the great veins with a specially devised clamp may result in a temporary stoppage of the heart, and occasionally perhaps a persisting slight slowing of the heart rate. In the perfused heart it was shown that excision of this region frequently, although by no means invariably, results in transitory stoppage of the parts of the heart below it, which, after recovery, usually beat at a permanently slowed rate.[21] These experiments were performed before the node of Keith and Flack was described; there is not the slightest doubt, however, but that the sinus node was invariably included in the tissue removed. It happens not infrequently that this operation is followed by the disappearance of the as-vs pause, the auricles and ventricles contracting synchronously instead of in sequence. But of this particular subject more later.

RESULTS OF EXCISION OF THE NODE

Since the node was described in 1907, attention has been directed to the effects of removing the region containing it alone, as compared with the removal of other regions. The results reported seem to be most inconstant. Flack,[22] one of the discoverers of the node, and Jäger,[23] experimenting with the dog's and cat's hearts hearts *in situ*, report totally negative results when the nodal region is excised or destroyed by heat. These experiments were carefully controlled by histological examination.

21. This result differs materially from that previously reported by Langendorff and Lehmann (Arch. f. d. ges. Physiol., 1906, lxii, 352) but has been abundantly confirmed by others.

22. Flack: Arch. internat. de physiol., 1911, xi, 111.

23. Jäger: Deutsch. Arch. f. klin. Med., 1910, c, 1.

Magnus-Alsleben[24] also reports totally negative results in the perfused heart of the rabbit. Lohmann[25] applied formaldehyd solution to the region of the node and obtained a slowing of the heart rate. It is scarcely necessary to call attention to the obvious difficulty of localizing the effects so produced. Brandenburg and Hoffmann[26] have attempted the isolation of the nodal region by means of cold. They state that when this region is thus isolated there is always a sudden change in the rate and sequence of the heart beat. Their article is, however, full of statements which scarcely can be reconciled with their conclusions. For instance, they state that injury to the auricles may cause other parts of the auricles to become the pace-maker. One is inclined to ask the question: Does this not provide them with a means of accounting for exceptions to the rule? It is for the purpose of avoiding injury to the auricles that they use cold to isolate the various regions of the auricles; despite this fact, they find that if the sinus node be isolated on three sides of a quadrangle by means of cuts, cooling of the node still causes the changes in rate mentioned above. Why, one might ask, do not the parts of the auricle injured by the cuts in this case now determine the beat of the heart?

Quite recently Cohn and Kessel,[27] working with the perfused dog's heart, stated in a preliminary note that the last of four cuts removing a rectangular area containing the sinus node always causes stoppage with subsequent slowing, or at least subsequent slowing of the auricles, which never regain their former rapidity; that when the excision of the node is incomplete no change in rate results. They consequently conclude that the node is the pace-maker of the heart. In view of the obvious differences between these results and those obtained by myself working with Blackman, the experiments of Cohn and Kessel were repeated with certain modifications by Moorhouse.[19] Moorhouse studied the reaction of the perfused dog's heart after excision of two rectangular strips, one (a) containing the sinus node, the other (b) immediately below this, but still a part of the sinus reuniens. Fifty experiments in all were made, all with the greatest of care and with exacting controls. Inasmuch as the results obtained were almost identical in the case of strips (a), and (b) the conclusion was reached that there is a balance of rhythmical power through the caval portion of the sinus region. The nodal region is not more rhythmical than neighboring regions of the sinus reuniens.

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24. Magnus-Alsleben: Arch. f. exper. Pathol. u. Pharmakol., 1911, lxiv, 228.
25. Lohmann: Arch. f. d. ges. Physiol., 1908, cxxiii, 628.
26. Brandenburg and Hoffmann: Med. Klin., 1912, viii, 16.
27. Cohn and Kessel: The Archives Int. Med., 1911, vii, 226.

The final report of Cohn, Kessel and Mason[28] then appeared. It profoundly modified their preliminary statement, in that positive results, namely, stoppage and slowing of the auricles, were obtained in but 80 per cent. to 90 per cent. of the experiments. Nothwithstanding these negative results they still are of the opinion that their experiments prove the sinus node to be the pace-maker of the heart. In view, however, of the fact that exactly the same results are obtained and just as frequently when a square of tissue below the sinus node is excised as when a square of tissue containing the sinus node is excised, experiments of this kind cannot be said to prove the specificity of the sinus node in the matter of impulse initiation.

EVIDENCE FROM WARMING AND COOLING

Another method that has been used for the purpose of locating the pace-maker of the heart has been to determine the area, warming or cooling of which will alter the rate of the whole normally beating heart. This method was first employed in the study of the mammalian heart by McWilliam[14] in 1888. McWilliam states that "the application of slight heat locally to the terminal part of the vena cava superior gives a very marked acceleration in the rhythm of the whole heart. A similar slight local heating of the ventricular apex or any part of the ventricular substance gives no change in cardiac rate." No further details are given, so that the reader is left to infer whether or not McWilliam tested the effect of temperature on other parts of the auricles than the superior vena cava. However this may be, McWilliam's final conclusion is that in the cat and the dog the usual origin of contraction is in the venous wall. In 1905, Adam,[29] working in Langendorff's laboratory, reinvestigated this subject and found that localized moderate warming and cooling altered the heart rate only in an area lying between the mouths of the two cavae and extending in the form of a triangle to the base of the auricle. The most sensitive spot lay between the two veins, somewhat nearer to the lower. Now, after the discovery of the sinus node, the same method in the hands of Ganter and Zahn[30] reveals that the nodal region, as delimited by Koch, alone is sensitive to temperature changes, the region overlying the thickest part of the node being the most sensitive spot. Brandenburg and Hoffmann[26] have obtained practically the same results. Ganter and Zahn and Brandenburg and Hoffmann, of course, conclude that the node is the normal pace-maker. The former investigators suggest a curious hypothesis to account for their observation that one part of the node may be more sensitive than others. It is

28. Cohn, Kessel and Mason: Heart, 1912, iii, 311.
29. Adam: Pflüger's Arch. f. d. ges. Physiol., 1906, cxi, 607.
30. Ganter and Zahn: Pflüger's Arch. f. d. ges. Physiol., 1912, cxlv, 335.

obvious, therefore, that the method of warming and cooling also gives results that seem inconstant. By it the rate of the heart may be affected over the terminal portion of the superior cava, over the node and near the inferior cava. The results are, however, consistent in this respect, namely, that they have been obtained only within the limits of the sinus reuniens. Those who have employed the temperature method have overlooked one consideration which may prove to be of considerable importance, namely, the accessibility of the region of the sinus reuniens to the thermods employed. Both His and Keith and Flack[7] explicitly state, it will be recalled, that in the mammalian heart nearly all of the sinus recedes from the surface of the heart. To say the least, it is a rather remarkable coincidence that in the hands of recent investigators only the two regions that presumably remain at the surface of the auricles are affected by moderate temperature changes.

EVIDENCE FROM ELECTROCARDIOGRAPHIC STUDIES

Lewis[31] has recently shown that the action current of beats of the auricles of the dog's heart determined by electrical stimulation of various points on the surface of the auricles resembles in form the normal action current only when the point stimulated is in the vicinity of the sinus node. This observation is considered as almost final proof that the impulse normally starts from the sinus node. The interpretation of Lewis' results, however, is not as simple as it may seem. It is necessary to bear in mind, for instance, that possibly this is one of the regions where primitive sinus tissue appears on the surface of the auricles. Is it not also possible that the impulse is so conducted through the auricle, owing either to the existence of definite paths, or to the thickness of the tissue, which in the region of the sinus node is comparatively great, that the sinus node region becomes negative electrically before other parts of the auricles? But there is still another possibility which an analysis of Lewis' results seems almost to substantiate.

The discussion of this possibility is begun with the assumption that the impulse which causes the heart to beat starts in the sinus venosus and crosses the sinoauricular junction into the auricles at the most accessible point. Reference to the diagram (Fig. 2) shows that this point is just about where the sinus node lies. Now the amplitude of electrical changes associated with activity is largely dependent on the mass of tissue reacting. The sinus venosus in the cold-blooded heart is relatively large, yet even when the electrodes are placed directly on it the deflection shown by the string galvanometer is relatively small. Samoiloff,[32] for instance, does not seem to picture a sinus action current

31. Lewis: Heart, 1910-11, ii, 23.
32. Samoiloff: Pflüger's Arch. f. d. ges. Physiol., 1910, cxxxv, 417.

in his extensive study of the frog's heart. The sinus of the mammalian heart probably contains much less tissue relatively than that of the cold-blooded heart. The action current of the former should consequently be correspondingly smaller. It is, therefore, not surprising that as yet no one has obtained a wave on the electrocardiogram of warm-blooded animals assignable to activity of the sinus.

Bearing in mind these assumptions an analysis of Lewis' results reveals the following: In all cases in which the contraction was evoked by a stimulus placed immediately over the sinoauricular junction (sinus node) or anywhere on the superior vena cava side of it, the P wave obtained, that is, the wave of auricular activity, closely approximates the P wave of the normal heart beat. In other words the curve is normal when it is started at the place where the impulse normally enters the auricle, or at some point on the sinus above this place. It is abnormal when it is started on the auricle or possibly on the sinus below the point at which it normally enters the heart. Lewis' experiments indicate, therefore, that the impulses pass into the auricle by way of the sinoauricular junction; they do not force us to the conclusion that the sinus node is the pace-maker.

The foregoing discussion also might serve to account for the observation of Lewis, Oppenheimer and Oppenheimer[33] and of Wybauw,[34] that as a rule the point on the auricle first to become electronegative lies approximately over the region of the sinus node. For if the tissue of the sinus is small in amount, and for the most part submerged in the surrounding tissue, the point first to become negative would be the place where the impulse passes from the sinus into the auricle. It should also be mentioned that the points of primary negativity, as determined in these two investigations, do not exactly coincide. Furthermore, both record exceptions to the rule. These exceptions the authors consider of no significance. Yet to us it is obvious that if the sinus node has the specific function of starting the beat of the heart it should be possible to show that under normal circumstances it invariably performs this function. This the electrocardiographic studies have failed to demonstrate.

SIGNIFICANCE OF NODAL RHYTHM

We have thus far purposely omitted the discussion of a result very commonly obtained in experiments on the sinus region of the auricles, namely, a change in the sequence of the auricular and ventricular beats. This change consists in a shortening of the auriculoventricular interval, or, more usually, in the actual disappearance of this interval, the auricles and ventricles contracting at almost exactly the same moment. The

33. Lewis, Oppenheimer and Oppenheimer: Heart, 1910-11, ii, 147.
34. Wybauw: Arch. internat. de physiol., 1910, x, 78.

term nodal rhythm has been applied to this type of beat. It may appear suddenly or, occasionally, gradually after operations on the sinus region of the heart. It is assumed by those who consider the nodes of Keith and Flack and of Tawara the most highly rhythmical regions of the heart, that the synchronous a-v beat is the result of the usurpation by the auricular node of the function of setting the pace of the heart when the more highly rhythmical sinus node is excised. Inasmuch as the tissue of the auricular node resembles somewhat that of the sinus node, this change in the character of the beat is considered clear proof of the specialization of the so-called nodal tissue in the direction of rhythmicity. The argument leading to this conclusion, it will be seen, is based on two propositions, namely, first, that the removal of the sinus node always results in the transfer of impulse initiation to the auricular node, and, second, that during the so-called nodal rhythm the impulse starts in the auricular node. Neither of these propositions has as yet been proved. The first proposition is by no means a fact.

It is true that extensive removal of auricular tissue, such, for example, as the liberal excision of much of the tissue in the sinus region in the perfused heart[12] very frequently is followed by synchronous contractions of the auricles and ventricles. But simple excision of the sinus node alone rarely results in the appearance of nodal rhythm, and even when it does occur it may be only transitory, the normal or almost normal sequence often returning after a longer or shorter period of nodal rhythm. Nodal rhythm was but rarely seen in the experiments of Jaeger, Flack, Magnus-Alsleben, Cohn and Kessel, Moorhouse, etc. On the other hand, it is claimed that the abolition of the functional activity of the region of the sinus node by means of cold almost invariably produces nodal rhytm. One cannot help but feel, however, that the temperature effects were not as nicely localized as it is believed they were. Be that as it may, a perusal of the reports of these experiments shows clearly that removal of the sinus node by cold does not always result in nodal rhythm. Thus Ganter and Zahn[30] state that "after stopping the activity of the sinus node by means of cold the auricles and ventricles do not always beat exactly synchronously. The as-vs interval may have a positive or negative value." While Brandenburg and Hoffmann[26] state that occasionally after removing the sinus node by cold or by excision the synchronous beats of the auricles and ventricles may be transitory, and that the original normal sequence may again return.

But even if it be admitted for the purpose of argument that the auricular node is determining the beat of the chambers while they are beating synchronously, it would by no means follow that the auricular node normally is more rhythmical than all the rest of the superventricular parts with the exception of the sinus node. Might not the

nodal rhythm be due to a temporary loss of the reactivity of the whole of the auricles, temporary inhibition, if that term is preferred, resulting from the tampering with the auricles, and that until the auricles recover, the auricular node, or, better, the next lower heart segment, determines the heart beat. It may be added that with the return of the normal sequence it can be shown that the auricles are setting the pace, since further operations on the auricles, such as cutting[12] or cooling the region of the coronary sinus[35] many again change the sequence. It is not entirely irrelevant to add, in this connection, that auricular strips containing the auricular node are not nearly so rhythmical as strips made from other parts of the auricle not alone while the sequence is normal, but even when, as a result of the excision of the great veins, the chambers are beating synchronously. Thus a companion strip from the coronary sinus region made at such a time always beats faster than the strip containing the auricular node.

Neither has it been proved that during so-called nodal rhythm the auricular node invariably is setting the pace of the heart. Indeed, almost the only observation in favor of this view is the fact that the chambers beat approximately simultaneously,[36] whereas there is just as good evidence to show that at such times the sinus may still be setting the pace of the whole heart. It has just been mentioned that extensive excision of the region of the great veins in the perfused rabbit's heart often results in so-called nodal rhythm. In ten consecutive experiments in which this occurred the auriculoventricular bundle was cut with a pair of scissors. The scissors were inserted through the opening made by the excision of the veins, one blade on either side of the exposed auricular septum down into the ventricles. A cut thus made in a heart as small as the rabbit's must undoubtedly have injured the node of Tawara. Yet this cut never slowed the auricles, indeed it usually left their rate entirely unchanged; the ventricles on the other hand showed the slowing that usually follows section of the bundle of His. Be this as it may, there is no necessity for limiting explanations of the so-called nodal rhythm to the view that it can be produced only by impulses arising in the auricular node. Indeed, inspection of the progress of the contraction wave in cooled hearts at a time when as a result of liberal excision of the great veins the auricles and ventricles are beating synchronously, has frequently revealed another cause. It can be seen in such experiments that the contraction wave may start in the region of the coronary sinus, and travel so slowly through the neighboring tissues of the auricles that the distant auricular appendices contract quite as late as the ventricles. Reference

35. Zahn: Zentralbl. f. Physiol., 1912, xxvi, 495.

36. Brandenburg and Hoffmann and Ganter and Zahn state that cooking or warming the auricular node after excision of the sinus node changes the rate of the beat.

to Figure 2 indicates clearly how a cut of this kind by forcing the impulse to travel for a long distance through the auricular canal before it can gain access to the auricles might lengthen the sinoauricular pause and so cause it to approximate the auriculoventricular pause.

Another question suggests itself here, namely, if it is admitted that the only two parts of the auricles that have sufficiently high rates of rhythm to dominate the rhythm of the auricles are the sinus node and the auricular node, how is the fact to be explained that the change from the auricular type of beat to the auriculoventricular type frequently is gradual, the auriculoventricular pause shortening slowly until the two chambers finally beat together?

STOPPAGE FROM INCISION OF THE NODE

Finally, a word with regard to the significance of stoppage of the heart from incision of the node. In 1907, Hering[37] stated that a simple incision in the sulcus terminalis, which presumably involved the sinus node, stopped completely the beat of the supraventricular parts. This result was at once hailed by Keith and Flack as proof of their suggestion that the sinus node is the pace-maker of the heart. In the same year[12] attention was called to the fact that stoppage of the heart often follows operations on or sometimes even a mere touch anywhere on a rather large area of the auricles, and the view was then expressed that stoppage probably occurs only when the part stimulated is at the time determining the beat of the heart. Irrespective of what may be the fate of this suggestion, it is interesting to note that recent work[38] has completely failed to confirm Hering. Incision of the node in the perfused heart of the dog does not stop the heart, to the contrary, it accelerates the heart rate.

II. LOCALIZATION OF CONDUCTIVITY IN THE HEART

HISTORICAL

In the historical introduction to the first part of this paper reference was made to the earliest hypotheses that were advanced to account for the sequence of the auricles and ventricles. We will, therefore, confine our attention here to the development of our modern ideas with regard to the dependence of the ventricles on the auricles. It has been said that Kürschner, in 1850, suggested a very complex explanation of the dependence of the ventricles on the auricles. One part of this explanation is of more than passing interest with reference to the topic in hand. "It is," Kürschner says, "now generally assumed that the musculature of the auricles is completely separated from that of the ventricles. From a study of the tissue composing the valves, I encountered conditions

37. Hering: Pflüger's Arch. f. d. ges. Physiol., 1907, cxvi, 143.
38. See, for instance, Cohn, Kessel and Mason, etc.

which are opposed to this view; I found muscle fibers extending from the auricle over into the valves." In attempting to account for the sequence of the heart beat he then proceeds to say:

> The anatomical conditions of the heart are indeed such that a measurable interval of time can elapse between the contraction of the auricles and of the ventricles. The muscle fibers which pass from auricle into the venous valves contain the organic basis of this phenomenon. . . . They cannot contract without supplying a stimulus to the ventricles. The contraction of the auricles must, therefore, determine the contraction of the ventricles.

Obviously, Kürschner might be said to have been the first investigator to have shown that "the musculature of the auricles is not completely separated from that of the ventricles." There are, however, two all-important differences between Kürschner's point of view and the accepted point of view of to-day. Although the valve musculature is described by Kürschner as extending over the auriculoventricular junction, it is not in the location of the connecting muscle band, as we now know it, nor does the valve musculature fuse with the musculature of the ventricles.

Over a quarter of a century later, in 1876, we find recorded what has developed into the second claim to the demonstration of the crossing of the musculature of the auricles into the ventricles. In that year Paladino[39] wrote as follows:

> The muscle layer of the sinus or auricle where it reaches the level of the auriculoventricular orifice loses the external circular layer of fibers, which stop, and is continued by the longitudinal fibers and the middle circular fibers downward to the interior of the valve leaflets . . . Of these fibers, the longitudinal terminate in the tendons of the second and third order . . . *And some tendons pass directly upon the walls of the ventricles*, where by means of flattened muscle bundles, which are inserted upon the valve leaflets, *they break up into small tendons.*

In 1910, Paladino, on the basis of passages similar to the one quoted above, pleads to have his name connected with that of the discoverer of the auriculoventricular bundle, as having demonstrated a muscular connection between the auricles and ventricles. As a matter of fact, a few authors have actually heeded this plea. It is obvious, however, that the criticism we have applied to Kürschner's work applies with equal force to the work of Paladino;[39, 17] no discrete definitely localized bundle is described, but rather scattered bundles in the valves, and there is no fusion of muscle bundles with the musculature of the ventricles.

In 1892-3, there appeared two articles by Kent,[40] which seem to represent the first of the recent attempts to determine whether or not the musculature of the auricles and of the ventricles are completely separated

39. Paladino: Arch. ital. d. biol., 1910, liii, 47.

40. Kent: Proc. Physiol. Soc. Nov. 12, 1892, and Jour. of Physiol., 1893, xiv, 233.

by connective tissue. Owing to the existence of some difference of opinion as to the exact significance of Kent's work in the development of this subject,[41] his results will be given as nearly as possible in his own words. In the adult animal (rat) a ". . . connecting sheet of muscle . . . is met with over a considerable area of the a-v groove; thus it may be mentioned that frequently in a single coronal section the connection may be seen between the outer (left) wall of the left ventricle and the left auricle, between the septum ventriculorum and the auricle, and between the right wall of the right ventricle and the right auricle." Describing a coronal section passing through the *junction of the left auricle with the left ventricle* of the heart of the newly-born rat, Kent says:

> . . . at about the center of the isthmus[42] the auricular fibers are seen to sweep freely down into the substance of the ventricular wall." "In the young rabbit of two days old . . . auricular fibers are seen sweeping down to the outer side of the fibrous ring, and become continuous with bundles belonging to the ventricular system. The connection also exists on the right side of the heart . . . and also in the septum to the right side of the ring bearing the mitral valve." In the monkey "the fibrous ring has attained a very perfect development and it is only here and there that places can be found to show the passage of muscular fibers across the groove.

ANATOMY OF THE AURICULOVENTRICULAR BUNDLE

In 1893, His called attention to the existence in the heart of a number of mammals of a single muscle bundle located in the posterior part of the septum and extending across the auriculoventricular junction obliquely from above and behind, downward and forward. In a review written in 1899, His[43] correctly refers to the bearing of Kent's work on his in the following terms:

> In man, indeed in mammals in general, a layer of connective tissue grows in between the muscle walls of the ventricles and auricles and separates these parts almost completely. Nevertheless muscle fibers have been found in this layer (Stanley Kent) and I myself have demonstrated a bundle present in mammals as well as in man, which passes from the posterior wall of the right auricle down to the ventricular septum.

While the existence of this single bundle, now usually and correctly designated the bundle of His,[17] has since been abundantly confirmed, the more recent work by Humblet, Retzer, Breaunig, Tawara, etc., has added much to His' original description. Much more, although not enough yet, is now known of its origin in the auricles, of its mode of determination in the ventricles and of the histology of its various parts. Overlooking

41. Meltzer: Med. Rec., New York, 1909, May 22, p. 873; also Nov. 27, p. 914.

42. It should be noted that the term "isthmus" as used here could not and was not by Kent intended to be synonymous with septum, since the section is from the junction of the left auricle with the left ventricle. Compare with Meltzer, loc. cit., note 41.

43. His: Deutsch. Arch. f. klin. Med., 1899, lxiv, 316.

for the present certain details on which opinion is as yet divided, the system connecting the auricles with the ventricles may be described briefly as follows:

It begins in the auricle in the posterior part of the septum, just above the auriculoventricular junction, and just anterior to and in the floor of the coronary sinus. Some authors describe a very close connection between the node and the auricular tissue. According to Cohn,[44] for example, it would seem that there is a general transition of auricular fibers into the characteristic nodal fibers. The number of fibers forming the connection, however, varies. "There may be a great many, closely packed together, the strands separated by masses of connective tissue; or there may be but a few rather thinner fibers with only delicate connective tissue strands between." The node of Tawara, into which these strands flow, is composed of characteristic branching and anastomosing cells which possibly were seen by Kent. Beyond the node the bundle, now compact and slender and taking on the characteristics of Purkinje cells, crosses the auriculoventricular junction and, continuing its course downward and forward, comes to lie on the upper edge of the muscular septum of the ventricles where it joins with the membranous part. The subsequent course of the conducting system is probably familiar to all. It can be best and indeed strikingly demonstrated by means of the injection method of Lhamon.[45] Lhamon has shown that when a colored injection fluid is forced through a hypodermic needle into the conducting system it will, owing to the connective tissue sheath, remain in that system and flow even into its ultimate branches. It is thus possible to make very evident the division of the main bundle into two limbs, a right and a left, the subendocardial course of these limbs down the respective sides of the ventricular septum, their branching into secondary twigs, some of which pass by way of the false tendons cross the cavities of the ventricles to the papillary muscles, and their further branching into an anastomosing network, the ultimate fasciculi of which dip down into the myocardium, and gradually change into fibers of the ventricular type, the individual fibers eventually terminating in a most interesting way in the conical point of a fasciculus of heart muscle.

Comparative anatomy and embryology, too, have added much to the significance of the His-Tawara system. Keith and Flack, in 1907, showed that in the simplest form of vertebrate heart a portion of the auricular canal, that part of the heart which in primitive forms joins the sinus with the ventricle, extends down into, or is invaginated into the ventricles. This invaginated part forms an isolated layer beneath the auriculoventricular valves. It is assumed in the primitive mammalian

44. Cohn: Heart, 1909-10, i, 172.
45. Lhamon: Am. Jour. Anat., 1912, xiii, 55.

heart that complete muscular connection between the auricles and ventricles exists around the whole auriculoventricular junction. As we ascend the animal scale, however, the invaginated portion of the auricular canal is encroached on more and more by the growth of connective tissue, until there is left only a small part of this musculature; it forms the auriculoventricular bundle. However, in certain animals, the rat, for example, auricular and ventricular fibers appear to come into close apposition in other places, especially in the right lateral auriculoventricular region. This, Keith and Flack venture to suggest, represents "one of the connections described by Stanley Kent. This close apposition, however, cannot be looked on as a connection; the auriculoventricular bundle is to be regarded as the sole connection between the auricular canal and the ventricle."

Mall[46] has studied the development of the auriculoventricular bundle in human embryos. At very early stages (embryo 3.9 mm.) the auricular canal forms a complete muscular connection between the sinus and the ventricle. Soon, however, as the result of the formation of subendocardial cushions of connective tissue, this ring becomes separated into a number of bundles, amongst which can be recognized at this time one occupying the same position and course as the auriculoventricular bundle in the adult. "The additional strips," Mall says, "may be of significance in view of Romberg's and Kent's observation." Kent found such bundles in the left wall of the heart as well as in the right wall in rats and rabbits. It is possible that some of these strips may be constant, or they may be variations. "At any rate," he goes on to say, "their presence has not been established as has the atrioventricular bundle of His." The auriculoventricular bundle, consequently, is not a structure of recent development; rather, it is a part of the wall of the primitive tube from which the heart is evolved. This fact, as has been said, should have some weight in inferring the function of the bundle from its structure; despite the great changes in, and the apparent complication of, the adult mammalian heart, it still preserves its primitive arrangement.

PHYSIOLOGY OF THE AURICULOVENTRICULAR BUNDLE

Considering now the physiological aspects of the problem of localizing conduction from auricles to ventricles in the warm-blooded heart, the view which held sway previous to 1893 practically universally was that the correlation of the work of the auricles and ventricles was affected through nerves crossing the auriculoventricular junction. An excellent idea of the point of view held by the physiologists of this period may be conveyed by a quotation from an article by Tigerstedt[47] in which are

46. Mall: Am. Jour. Anat., 1912, xiii, 284.
47. Tigerstedt: Arch. f. Physiol., 1884, p. 497.

recorded the results of severing completely by means of a cut the connection of the auricles with the ventricles in the rabbit's heart. In order to make this quotation clear, it should be preceded by the statement that in the previous year Wooldridge[48] had accomplished the same separation by means of a mass ligature, with the result that the auricles and ventricles contracted independently of each other. Tigerstedt says:

> Wooldridge in dogs and cats performed the experiment of severing the *nervous connection* [italics ours] between the auricles and ventricles, that is to say he made the Stannius experiment on the warm-blooded heart.
>
> And again, by way of introduction to his experiments Tigerstedt says: The interesting results obtained by Wooldridge by means of his ligature made it necessary to repeat with more rigorous methods the separation of the *nervous connections* [italics ours] between the ventricles and auricles because it might be objected that the ligature failed to divide all of the nerve fibers between the auricles and ventricles . . .

This assumption seemed justifiable in view of the prevailing opinion that there was no muscular connection between the auricles and ventricles.

In the same paper in which Kent described muscular connections in various parts of the auriculoventricular junction, mention is made of some experiments in which a clamp was applied to the auriculoventricular groove of the mammalian heart just as Gaskell had done in the frog's heart. Kent states without giving the records "that almost precisely similar results [to those of Gaskell] were obtained." It may, therefore, be assumed that he obtained with this clamp the various stages of partial and complete block. The experiments of Wooldridge, Tigerstedt and Kent, therefore, demonstrate conclusively that in the mammalian heart the impulse which causes the ventricles to beat arises in the auricles and crosses the auriculoventricular junction; the old view that the sequence is due to stimulation by the blood is disproved. Shortly after His[49] described the muscular bundle that bears his name, he read before the Physiological Congress a paper describing the results of cutting this bundle. No final report of these experiments has ever appeared, and it was not until the bundle of His was redescribed in 1904 by Retzer, by Breaunig and by Humblet that the attention of physiologists was attracted to this structure. Then Humblet[50] showed, as had been shown by His, that section of practically nothing but the bundle in the perfused heart results in complete dissociation of the auricles and ventricles. A year later the same observation was made by Hering,[51] also in the perfused heart. Simultaneously the results were published of compressing in a specially devised clamp practically nothing but the His bundle in

48. Wooldridge: Arch. f. Physiol., 1883, p. 522.
49. His: Zentralbl. f. Physiol., 1895, ix, 469.
50. Humblet: Arch. internat. d. physiol., 1904, c, 278.
51. Hering: Pflüger's Arch. f. d. ges. Physiol., 1905, cvii, 97.

the heart *in situ*.[52] The results thus obtained were similar to those following compression in a clamp of all of the auriculoventricular junction in both cold and warm-blooded animals. These results have since been abundantly confirmed. Practically the only conflicting evidence comes from the Bern laboratory. Lomakina[53] says that dissociation of the auricles and ventricles can be obtained by dividing the superficial macroscopic nerves in the auriculoventricular groove. This result has not been confirmed. Paukul[54] and Kronecker[55] state that crushing the auriculoventricular bundle in rabbits does not block the passage of the impulse into the ventricles. Cohn and Trendelenburg[56] have offered what seems to be a plausible explanation of this anomalous result. They have found that in the rabbit the bundle may not pass into the ventricle as a single strand, but may divide into several strands which spread out after the fashion of a fan. They suggest that some of these branches probably escaped inclusion in the ligature as placed by Paukul and Kronecker. We are, therefore, justified in asserting that experiments of the kind thus far described prove that the only *functional* connection between the auricles and ventricles is by way of the His bundle.

It is not, however, unreasonable to maintain that other connections exist, such, for example, as were described by Kent, that under ordinary circumstances such other connections are dormant, and that in the course of the few hours the heart is under observation in experiments as ordinarily performed these connections cannot develop their activity sufficiently to perform vicariously the function of the His bundle. This objection seems to be met by those instances of chronic heart-block in man, in which a lesion, more or less accurately limited to the region of the auriculoventricular bundle, undoubtedly has served to block permanently the passage of the excitation wave through the auriculoventricular junction. Nevertheless, clinical observations, even when confirmed by post-mortem findings, do not carry the conviction of a clean-cut experiment; there is always the possibility that tissues other than those found to be diseased may be the seat of pathological processes, which, however, have escaped detection. This objection has been removed by some experiments in which heart-block was produced by crushing under aseptic precautions the auriculoventricular bundle in the clamp above alluded to and then allowing the animals (dogs) to live.[57] Two of these animals survived the operation 320 and 343 days, respectively. During this entire period there was complete dissociation of the auricles and

52. Erlanger: Zentralbl. f. Physiol., 1905, xix, 9; also Jour. Exper. Med., 1906, viii, 8.
53. Lomakina: Ztschr. f. Physiol., 1900, xxxix, 377.
54. Paukul: Ztschr. f. Physiol., 1908, li, 177.
55. Kronecker: Brit. Med. Jour., 1910, i, 135.
56. Cohn and Trendelenburg: Pflüger's Arch. f. d. ges. Physiol., 1910, cxxxi, 1.
57. Erlanger and Blackman: Heart, 1910, i, 177.

ventricles. We may conclude, therefore, that there is no connection between the auricles and ventricles that can vicariously assume the functions of the bundle of His. Thus the path of conduction across the auriculoventricular groove is narrowed down to the auriculoventricular bundle.

Now that we know that the auriculoventricular bundle is as much a part of the primitive heart tube as any other part of the heart, we could scarcely expect conduction in it to differ from conduction in the rest of the heart, the presence in the bundle of a considerable amount of nerve tissue to the contrary notwithstanding.[58] Nevertheless, the question has been asked, Is it possible to carry further the localization of impulse conduction in this region by determining whether it is through muscle or through nerve? The results of experimentation in this direction, though suggestive, are still far from being conclusive. The fact that in animals regeneration of function does not occur even in the course of a year after complete section of the auriculoventricular bundle, would seem to indicate that nerves are not concerned with the process of impulse conduction. This conclusion is based on the usually accepted view with regard to the power of regeneration of heart muscle and of nerve. Wounds of heart muscle heal by the formation of scar tissue; the muscle cells show little, if any, tendency to regenerate.[59] On the other hand, it is well known that in due time nerves will regenerate. This is true not alone of nerve trunks, but also of nerve plexuses, such, for example, as the mesenteric plexus.[60]

When our attention was first directed to this subject a perusal of the literature revealed that regeneration of nerve and of muscle, in so far as it pertains to the heart, had been studied by histological methods only. So far as could be ascertained, no effort had been made to determine whether restoration of conductivity across a healed wound of the heart will occur. Consequently the attempt was made to determine whether a functional connection between the auricles and ventricles could be established by uniting contiguous surfaces of the auricles and ventricles, which have been denuded of their epicardial covering. This attempt failed. It was not, however, considered conclusive because of the great difficulty of obtaining close apposition of thin-walled auricle to ventricle. For the purpose of putting this question of regeneration to a crucial test, the following experiment was then made:[61]

Under aseptic precautions the tip of the auricular appendix of the dog's heart was crushed in a clamp so as to sever it functionally from the auricle proper excepting a narrow strip along one edge. The tip was not completely isolated, since it was feared that then atrophy of the functionless part would occur and

58. Wilson: Anat. Rec., 1909, viii, 262.
59. See Thorel: Lubarsch and Ostertag's Ergebnisse, 1903, ix, 861.
60. Meek: Am. Jour. Physiol., 1910, xxv, 367.
61. Erlanger: Am. Jour. Physiol., 1909, xxiv, 375.

would interfere with the interpretation of the results. The animal was then allowed to live some 130 days. Then the tissue of the auricle was crushed in a line extending out to the tip of the auricle and intersecting at right angles the old line of crush. By this procedure the appendix is divided into two triangular areas, one separated from the heart by the old and new lines of crush, the other still functionally connected with the heart through the undestroyed isthmus at the edge of the auricle. By using the second area as a control, it was then found that functional connection between the first area and the heart had not developed. Histological examination revealed that heart muscle had not grown across the old contusion, whereas nerve could be traced from one side to the other. The presence of this nervous union obviously did not suffice for the conduction of the impulse.

Such a result makes it very probable, although it does not prove, that the muscular rather than the nervous elements of the His bundle carry the impulse from the auricles to the ventricles. In support of this conclusion it might be added that Cullis and Dixon[62] have shown that the application of a 5 per cent. solution of cocain to the bundle of His does not produce heart-block, although all of the nerve fibers with which the cocain comes into contact would certainly be paralyzed.

We have yet to consider conduction within the ventricles. Is the impulse delivered by the His bundle to the ventricular musculature at or near the point where it crosses the auriculoventricular junction, or must it first traverse the entire complicated system described by Tawara, DeWitt, Lhaman and others?

These questions were first formulated only a few years ago and are still the subject of discussion. The experiments devised to answer them are as yet but little beyond the formative stage. Considering first the results of cutting both of the main divisions of the bundle of His, the general statement may be made that the mass of evidence points to a union of the bundle fibers with the ventricular musculature below the bifurcation. Thus Barker and Hirschfelder[63] have shown in the dog that cutting the left branch usually gives complete block. In the one case in this series of experiments in which block did not appear, both the ventricles seemed to contract coordinately. Eppinger and Rothberger[64] state that cutting one limb produces an obvious effect at once; the two ventricles seem to alternate. Complete block, however, did not follow section of one limb, but only section of both. The difference in the results of these two investigations is probably merely one of degree. The experiments of Biggs, though, are not in harmony with either of the foregoing researches. Biggs[65] finds that in the rabbit, section of all branches of the bundle of His does not cause heart block, and he furthermore finds, as do also Cullis and Dixon, working with the same animal, that retrograde conduction may sometimes occur after section of the

62. Cullis and Dixon: Jour. Physiol., 1911, xlii, 156.
63. Barker and Hirschfelder: The Archives Int. Med., 1909, iv, 192.
64. Eppinger and Rothberger: Centralbl. f. Physiol., 1911, xxiv, 1055.
65. Biggs: Brit. Med. Jour., 1908, i, 1419.

bundle. This result leads one to suspect either that these investigators failed to cut all of the branches of the bundle, despite the fact that both seem to have been aware of the variations that occur in the bundle of the rabbit's heart, or that the auricles were stimulated mechanically by the ventricles, as Cullis and Dixon seem inclined to believe. So far as present purposes are concerned the results, however, indicate that the termination of the His bundle lies some distance beyond its bifurcation.

How much farther on its course into the ventricles does the impulse remain in the conducting system? Tawara is of the opinion that the impulse is carried in the bundles to the most distant parts of the ventricles; indeed, to the papillary muscles first. The moment of contraction of the papillary muscle, it might therefore be suspected, should serve to throw some light on this question. Do they contract before, with or after the body of the ventricles? Until quite recently it was regarded as probable that the papillary muscles contract synchronously with or possibly a moment later than the body of the ventricles.[66] The reinvestigation of this subject that has been stimulated by the suggestions of the anatomists has as yet led only to conflicting results,[67] which need not be reviewed here.

It has thus far been assumed that the secondary branches of the His-Tawara system, which, as has been said, are composed of Purkinje tissue, carry the impulse through the ventricles. This assumption is based on anatomical observations and on the observation, to which reference has just been made, that section of the His bundle, or of its two main branches, produces heart block. In view of the possibility of misinterpreting the results so obtained, it was thought that it would be interesting to have some definite information with regard to conduction in the ventricular portion in the His-Tawara system. The first attempts in this direction seem to have been made by Hering.[68] He cut the auriculoventricular bundle in the dog and then stimulated the cut surface. More recently Cullis and Dixon applied electrodes directly over the intact bundle in the rabbit's heart. While the results obtained in both of these researches indicate that the bundle responds to direct stimulation, the very close proximity of the ventricular musculature, which could not have been more than 1 mm. away from the electrodes, renders the conclusions somewhat uncertain.

It has been said that some of the branches of the His-Tawara system cross the cavities of the ventricles by way of the false tendons or interventricular bands. The studies of Petersen, which were confirmatory of Miss DeWitt's observations, demonstrate that some of these interven-

66. For a discussion of this subject see Shafer's Text Book of Physiology, London, 1900, ii, 10.

67. Saltzmann: Skand. Arch., 1908, xx, 233; Hering: Pflüger's Arch. f. d. ges. Physiol., 1909, cxxvi, 225.

68. Hering: Pflüger's Arch. f. d. ges. Physiol., 1910, cxxxi, 572.

tricular bands in the beef's heart consist of Purkinje fibers and connective tissue exclusively. Thus the way was opened to a conclusive reply to the question of irritability and conductivity in the Purkinje system. It has been determined in the perfused beef's heart that stimulation of false tendons, which were found by subsequent histological examination to be entirely free of heart muscle proper and to contain as irritable structure only Purkinje tissue, causes a contraction of the ventricles.[69] There could be no question in these experiments of an escape of the current to the ventricular musculature, since often the electrodes were applied to the false tendons a centimeter or more from their insertion into the ventricular wall, while the strength of the stimulus eliciting a reply from the false tendon in many cases did not suffice to elicit a reply when applied directly to the ventricular wall.

This method has also served to shed some light on other important matters. By means of it, it has been found possible to show that impulses carried to the ventricles by way of the His-Tawara system are not of necessity delivered first to the papillary muscles. If a false tendon be divided near its middle and the two stumps be stimulated separately, the ventricles will, in both cases, contract. Assuming that in both cases the impulse is delivered to the papillary muscles, the distance it must travel by way of the papillary stump of the false tendon would be much shorter than the distance by way of the septal stump, and we should expect to find a corresponding difference in the latent period of the ventricular contraction. As a matter of fact, however, the latencies have, as nearly as can be determined, the same duration.

However this may be, it can be shown that the central stump of the false tendon probably does not terminate close to its insertion into the septum. It is well known that practically all of the main branches of the His bundle lie immediately under the endocardium, the terminal branches alone apparently dipping into the depths of the myocardium. It, therefore, seems justifiable to assume that a cut a couple of millimeters deep circumscribing the septal insertion of a false tendon severs all of the Purkinje tissue connected therewith, excepting that of the terminal branches. Such a cut has been found to annul the response of the ventricles to stimulation of the circumscribed false tendon, while the mere ringing of an area of heart muscle does not of itself annul the irritability of the enclosed area. At least two interpretations of this result are possible: (1) Either the immediate connections of the false tendon with the subjacent heart tissue are not extensive enough to carry the impulse, that is to say, a relatively complete block results from the operation; or (2) the impulse before it is delivered to the myocardium must first be carried to some distant point by the large subendocardial

69. Erlanger: Am. Jour. Physiol., 1912, xxx, 395.

strands of the conducting system. It remains for future work to settle this matter.

Another point of some interest in connection with the localization of conduction is the following: It is well known that impulses are conducted in either direction between the auricles and ventricles. Consequently it should be possible to show that the conducting system, if properly so-called, will carry impulses in either direction. Experiments with false tendons have shown not alone that this is the case, but also that the impulses are carried at the same rate in either direction.

CONCLUSION

The first conclusion one is apt to draw from a review of the work that has been done in the effort to localize the site of impulse initiation and conduction is that the former subject at least is in a state of hopeless confusion. I venture to predict, however, that when the last word has been said, the structure and function of the mammalian heart will be found to be almost identical with the structure and function of the heart of cold-blooded animals, of which the heart of the eel, owing to its simplicity and to the care with which it has been studied, may serve as a type. The normal sequence of the eel's heart differs in no wise from that in other hearts, sinus, auricles and ventricles contracting in the order given, which is also the order of the rhythm of these parts when isolated. Under the eye it can be seen that the contraction begins in the venous part of the sinus. It passes from the sinus directly into the nearest part of the auricle and then spreads over the auricular tissue, whence it passes into the auricular canal through which it finally involves the central fibers of the ventricle. "The rhythmical power of each segment of the heart varies inversely as does the distance from the sinus." The auricular canal, which might almost be regarded as a prolongation of the sinus tissue, possesses a much higher rhythmical power than the auricles. Therefore, in the mammalian heart we should expect the rhythmicity of the sinoventricular bundle to be exceeded only by that of the sinus region, and this seems to be to the case. In the eel's heart the impulse normally reaches the ventricle by way of the auricle, but it can reach the ventricle directly by way of the auricular canal also. In the latter event the auricles do not contract. The anatomical possibility of this path has been all but worked out in the mammalian heart. It is believed that the finding of such a path would help materially toward accounting for the appearance of nodal rhythm following excision of the upper part of the sinus region as well as for many other of the phenomena noted in this paper. In any event, we cannot afford, in the interpretation of the functions of the heart of man, to ignore the results of investigation in the field of comparative physiology.